(19) Europäisches Patentamt
European Patent Office
Office ur péen des brevets

(11) EP 0 978 512 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
09.02.2000 Bulletin 2000/06

(21) Application number: **98401944.8**

(22) Date of filing: **29.07.1998**

(51) Int. Cl.[7]: **C07D 295/088**, C07C 211/08, C07D 211/04, C07D 295/185, C07D 211/62, C07D 211/70, C07D 207/20, A61K 31/13, A61K 31/40, A61K 31/445, A61K 31/495

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV MK RO SI

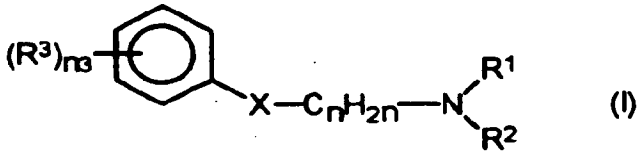
(71) Applicant:
SOCIETE CIVILE BIOPROJET
F-75003 Paris (FR)

(72) Inventors:
- **Schwartz, Jean-Charles**
  75014 Paris (FR)
- **Arrang, Jean-Michel**
  91419 Dourdan (FR)
- **Garbarg, Monique**
  75017 Paris (FR)
- **Lecomte, Jeanne-Marie**
  75003 Paris (FR)
- **Ligneau, Xavier**
  75013 Paris (FR)
- **Schunack, Walter G.**
  14129 Berlin (DE)
- **Stark, Holger**
  12157 Berlin (DE)
- **Ganellin, Charon Robin**
  Welwyn, Hert AL6 OTD (GB)
- **Leurquin, Fabien**
  London E2 6DZ (GB)
- **Sigurd, Elz**
  12107 Berlin (DE)

(74) Representative:
Le Guen, Gérard et al
CABINET LAVOIX
2, place d'Estienne d'Orves
75441 Paris Cédex 09 (FR)

(54) Non-imidazole aryloxy (or arylthio) alkylamines as histamine H3-receptor antagonists and their therapeutic applications

(57) Compounds of formula (I):



(I)

and their use for preparing medicaments acting as antagonists at the H_3-receptors of histamine.

EP 0 978 512 A1

Description

[0001] The present invention relates to novel aryloxy (or arylthio) alkylamines, to their preparation and to their therapeutic applications.

[0002] Antagonists of histamine H_3 receptor are known especially to increase synthesis and release of cerebral histamine. Through this mechanism, they induce an extended wakefullness, an improvement in cognitive processes, a reduction in food intake and a normalization of vestibular reflexes (Schwartz et al., Physiol. Rev., 1991, 71; 1-51).

[0003] Whence these agents are potentially useful in several central nervous system disorders such as Alzheimer disease, mood and attention alterations, cognitive deficits in psychiatric pathologies, obesity, vertigo and motion sickness.

[0004] All the H_3 receptor antagonist compounds known so far resemble histamine in possessing an imidazole ring (Ganellin et al., Ars Pharmaceutica, 1995, 36:3, 455-468; Stark et al., Drug of the Future, 1996, 21(5), 507-520).,

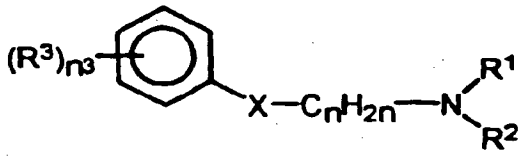
[0005] Nevertheless, such imidazole derivatives may show drawbacks such as poor blood-brain barrier penetration and/or some hepatic and ocular toxicities. These drawbacks, which can prevent their therapeutic development, appear to be linked to the presence of an imidazole ring substituted by a hydrophobic chain.

[0006] Attempts to develop H_3 receptor antagonists without an imidazole ring have up to now been unsuccessful, the compounds being of low potency.

[0007] In this respect, non-imidazole compounds such as betahistine (J-M. Arrang et al., Eur. J. Pharmacol. 1985, 111: 72-84), phencyclidine (J-M. Arrang et al., Eur. J. Pharmacol. 1988, 157: 31-35), dimaprit (J-C Schwartz et al., Agents Actions 1990, 30: 13-23), clozapine (M. Kathmann et al., Psychopharmacology 1994, 116: 464-468), and sesquiterpenes (M. Takigawa et al., JP 06 345 642 (20 Dec 1994)) were suggested to display H_3-receptor antagonism but all these compounds have only very low potency.

[0008] The present invention provides new compounds, the structure of which do not contain an imidazole moiety, which are useful as histamine H_3-receptor antagonists while avoiding the above-mentioned drawbacks of the known H_3-antagonists.

[0009] The compounds of the invention have the following general formula (I):



(I)

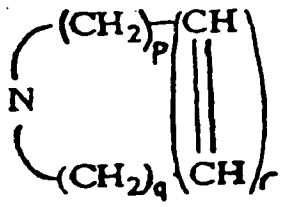
in which:

- C_nH_{2n} is a linear or branched hydrocarbon chain with n ranging from 2 to 8;
- X is an oxygen or sulfur atom;
- R^1 and R^2 may be identical or different and represent each independently
  - a lower alkyl or cycloalkyl, or taken together with the nitrogen atom to which they are attached,
  - a saturated nitrogen-containing ring

i) 

with m ranging from 4 to 7, or

- an unsaturated nitrogen-containing ring

ii) 

with p, q and r being 1 to 3 independently, such nitrogen-containing ring i) or ii) being unsubstituted or substituted by one or more lower alkyl or cycloalkyl, or carboalkoxy groups, or

- a morpholino group, or
- a N-substituted piperazino group:

with R being a lower alkyl, an alkanoyl or an optionally substituted phenyl group;

— n_3 is an integer from 0 to 5;
— R^3 represents each independently

- a halogen atom,
- a lower alkyl or cycloalkyl, a trifluoromethyl, aryl, alkoxy, aryloxy, nitro, formyl, alkanoyl, aroyl, arylalkanoyl, amino, carboxamido, cyano, alkyloximino, aryloximino, α-hydroxyalkyl, alkenyl, alkynyl, sulphamido, sulfamoyl, carboxamide, carboalkoxy, arylalkyl or oxime group,
- or taken together with the carbon atoms of the phenyl ring to which it is fused, a 5- or 6-membered saturated or unsaturated ring or a benzene ring.

[0010] The invention also relates to the addition salts which the compounds form with pharmaceutically acceptable acids. The pharmaceutically acceptable salts comprise the nontoxic salt of inorganic or organic acids. Examples of these salts include the hydrochloride, the hydrobromide or the hydrogen maleate or hydrogen oxalate.

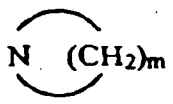
[0011] The present invention also encompasses the hydrates of the compounds, the hydrated salts of these compounds and the polymorphic crystalline structures. When the compounds can exist in one or a number of isomeric forms according to the number of asymmetric centres in the molecule, the invention relates both to all the optical isomers and to their racemic modifications and the corresponding diastereoisomers. The separation of the diastereoisomers and/or of the optical isomers can be carried out according to methods known per se.

[0012] According to the invention, lower alkyl or cycloalkyl is intended to mean a linear or branched alkyl group containing from 1 to 6 carbon atoms, or a saturated carbocycle containing 3 to 6 carbon atoms.

[0013] Typically examples of lower alkyl are methyl, ethyl, propyl, isopropyl and butyl groups.

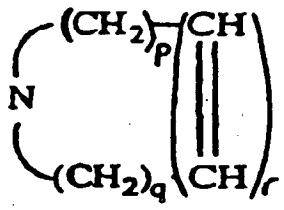
[0014] A preferred group of compounds according to the invention comprises those with R^1 and R^2 representing independently a lower alkyl group, especially an ethyl group.

[0015] Preferred compounds are also those of formula (I) in which R^1 and R^2 taken together with the nitrogen atom to which they are attached, form a saturated nitrogen-containing ring:

i) 

especially with m being 4, 5 or 6, optionally substituted with an alkyl group, preferably a methyl group.

[0016] Another preferred group of compounds comprises compounds (I) in which R^1 and R^2 taken together with the nitrogen atom to which they are attached, form an unsaturated nitrogen-containing ring:

ii) 

especially with p, q, and r being 1 or 2. In this group, more preferred compounds are those with p being 2 and q and r each being 1.

[0017] Typical example of $-NR^1R^2$ representing a N-substituted piperazino group is N-acetylpiperazino.

[0018] A preferred group of compounds according to the invention is the group composed of compounds of formula (I) in which X is an oxygen atom.

[0019] Another preferred group of compounds comprises compounds (I) in which $-C_nH_{2n}-$ is a linear chain $-(CH_2)_n-$ with n being as previously defined.

[0020] Preferred compounds are also those with n varying from 3 to 5, and with n being more preferably 3.

[0021] A sub-class of compounds according to the invention comprises the compounds of formula (I) with n_3 being z r that is those having an unsubstituted phenyl moiety.

[0022] Another group of compounds according to the invention is composed of compounds containing one or more substituents R^3 which may be identical or different. In this group, the compounds having a mono- or di-substituted (n_3 = 1 or 2) phenyl moiety are preferred and those mono-substituted with one group R^3 as defined above in para-position are particularly preferred.

[0023] Among these compounds, (n_3 being 1) R^3 is preferably a halogen atom or a cyano, nitro, alkanoyl, alkyloximino or α-hydroxyalkyl group.

[0024] Still more preferred compounds are those with R^3 being CN, NO_2, $COCH_3$, COC_2H_5, $H_3C-C=N-OH$, $H_3C-CH-OH$.

[0025] R^3 being a halogen atom may be advantageously selected from fluorine, chlorine and bromine.

[0026] R^3 being an aryl group, may be especially a phenyl group.

[0027] In the other substituents R^3, the aryl moiety is advantageously a phenyl moiety.

[0028] R^3 being an aryloxy group may be especially a phenoxy group.

[0029] According to the invention, alkanoyl is intended to mean a group containing an alkyl moiety as defined above.

[0030] Typical examples of R^3 being an alkanoyl, aroyl or arylalkanoyl group are acetyl, butyryl and propionyl groups, benzoyl group or phenylacetyl group.

[0031] Typical examples of R^3 forming together with the carbon atoms of the phenyl ring to which it is fused, a saturated ring leads to 5,6,7,8-tetrahydronaphthyl or forming a benzene ring leads to a naphthyl moiety.

[0032] According to the invention, alkenyl or alkynyl group may contain advantageously from 1 to 8 carbon atoms, in particular from 1 to 6 carbon atoms and preferably 1 to 4 carbon atoms.

[0033] In carboalkoxy, carboxyamido or carboxamide groups, the hydrocarbon chain is saturated, linear or branched and contains an alkyl moiety as defined above.

[0034] In alkoxy, alkyloximino, arylalkyl or α-hydroxyalkyl group, the alkyl moiety is as previously defined also.

[0035] Particularly preferred compounds are:

1-(5-phenoxypentyl)-piperidine
1-(5-phenoxypentyl)-pyrrolidine
N-methyl-N-(5-phenoxypentyl)-ethylamine
1-(5-phenoxypentyl)-morpholine
N-(5-phenoxypentyl)-hexamethyleneimine
N-ethyl-N-(5-phenoxypentyl)-propylamine
1-(5-phenoxypentyl)-2-methyl-piperidine
1-(5-phenoxypentyl)-4-propyl-piperidine
1-(5-phenoxypentyl)-4-methyl-piperidine
1-(5-phenoxypentyl)-3-methyl-piperidine
1-acetyl-4-(5-phenoxypentyl)-piperazine
1-(5-phenoxypentyl)-3,5-trans-dimethyl-piperidine
1-(5-phenoxypentyl)-3,5-cis-dimethyl-piperidine

1-(5-phenoxypentyl)-2,6-cis-dimethyl-piperidine
4-carboethoxy-1-(5-phenoxypentyl)-piperidine
3-carboethoxy-1-(5-phenoxypentyl)-piperidine
1-(5-phenoxypentyl)-1,2,3,6-tetrahydropyridine
1-[5-(4-nitrophenoxy)-pentyl]-pyrrolidine
1-[5-(4-chlorophenoxy)-pentyl]-pyrrolidine
1-[5-(4-methoxyphenoxy)-pentyl]-pyrrolidine
1-[5-(4-methylphenoxy)-pentyl]-pyrrolidine
1-[5-(4-cyanophenoxy)-pentyl]-pyrrolidine
1-[5-(2-naphthyloxy)-pentyl]-pyrrolidine
1-[5-(1-naphthyloxy)-pentyl]-pyrrolidine
1-[5-(3-chlorophenoxy)-pentyl]-pyrrolidine
1-[5-(4-phenylphenoxy)-pentyl]-pyrrolidine
1-{5-[2-(5,6,7,8-tetrahydronaphthyl)-oxy]-pentyl}-pyrrolidine
1-[5-(3-phenylphenoxy)-pentyl]-pyrrolidine
1-(5-phenoxypentyl)-2,5-dihydropyrrole
1-{5-[1-(5,6,7,8-tetrahydronaphthyl)-oxy]-pentyl}-pyrrolidine
1-(4-phenoxybutyl)-pyrrolidine
1-(6-phenoxyhexyl)-pyrrolidine
1-(5-phenylthiopentyl)-pyrrolidine
1-(4-phenylthiobutyl)-pyrrolidine
1-(3-phenoxypropyl)-pyrrolidine
1-[5-(3-nitrophenoxy)-pentyl]-pyrrolidine
1-[5-(4-fluorophenoxy)-pentyl]-pyrrolidine
1-[5-(4-nitrophenoxy)-pentyl]-3-methyl-piperidine
1-[5-(4-acetylphenoxy)-pentyl]-pyrrolidine
1-[5-(4-aminophenoxy)-pentyl]-pyrrolidine
1-[5-(3-cyanophenoxy)-pentyl]-pyrrolidine
N-[3-(4-nitrophenoxy)-propyl]-diethylamine
N-[3-(4-cyanophenoxy)-propyl]-diethylamine
1-[5-(4-benzoylphenoxy)-pentyl]-pyrrolidine
1-{5-[4-(phenylacetyl)-phenoxy]-pentyl}-pyrrolidine
N-[3-(4-acetylphenoxy)-propyl]-diethylamine
1-[5-(4-acetamidophenoxy)-pentyl]-pyrrolidine
1-[5-(4-phenoxyphenoxy)-pentyl]-pyrrolidine
1-[5-(4-N-benzamidophenoxy)-pentyl]-pyrrolidine
1-{5-[4-(1-hydroxyethyl)-phenoxy]-pentyl}-pyrrolidine
1-[5-(4-cyanophenoxy)-pentyl]-diethylamine
1-[5-(4-cyanophenoxy)-pentyl]-piperidine
N-[5-(4-cyanophenoxy)-pentyl]-dimethylamine
N-[2-(4-cyanophenoxy)-ethyl]-diethylamine
N-[3-(4-cyanophenoxy)-propyl]-dimethylamine
N-[4-(4-cyanophenoxy)-butyl]-diethylamine
N-[5-(4-cyanophenoxy)-pentyl]-dipropylamine
1-[3-(4-cyanophenoxy)-propyl]-pyrrolidine
1-[3-(4-cyanophenoxy)-propyl]-piperidine
N-[3-(4-cyanophenoxy)-propyl]-hexamethyleneimine
N-[6-(4-cyanophenoxy)-hexyl]-diethylamine
N-[3-(4-cyanophenoxy)-propyl]-dipropylamine
N-3-[4-(1-hydroxyethyl)-phenoxy]-propyl-diethylamine
4-(3-diethylaminopropoxy)-acetophenone-oxime
1-[3-(4-acetylphenoxy)-propyl]-piperidine
1-[3-(4-acetylphenoxy)-propyl]-3-methyl-piperidine
1-[3-(4-acetylphenoxy)-propyl]-3,5-trans-dimethyl-piperidine
1-[3-(4-acetylphenoxy)-propyl]-4-methyl-piperidine
1-[3-(4-propionylphenoxy)-propyl]-piperidine
1-[3-(4-acetylphenoxy)-propyl]-3,5-cis-dimethyl-piperidine
1-[3-(4-formylphenoxy)-propyl]-piperidine

1-[3-(4-isobutyrylphenoxy)-propyl]-piperidine
N-[3-(4-propionylphenoxy)-propyl]-diethylamine
1-[3-(4-butyrylphenoxy)-propyl]-piperidine
1-[3-(4-acetylphenoxy)-propyl]-1,2,3,6-tetrahydropyridine

[0036] More preferred compounds are:

1-[5-(4-nitrophenoxy)-pentyl]-pyrrolidine
N-[3-(4-cyanophenoxy)-propyl]-diethylamine
N-[3-(4-acetylphenoxy)-propyl]-diethylamine
1-{5-[4-(1-hydroxyethyl)-phenoxy]-pentyl)-pyrrolidine
N-[4-(4-cyanophenoxy)-butyl]-diethylamine
1-[3-(4-cyanophenoxy)-propyl]-piperidine
N-[3-(4-cyanophenoxy)-propyl]-hexamethyleneimine
N-3-[4-(1-hydroxyethyl)-phenoxy]-propyl-diethylamine
4-(3-diethylaminopropoxy)-acetophenone-oxime
1-[3-(4-acetylphenoxy)-propyl]-3-methyl-piperidine
1-[3-(4-acetylphenoxy)-propyl]-4-methyl-piperidine
1-[3-(4-propionylphenoxy)-propyl]-piperidine

[0037] Compounds of formula (I) in which:

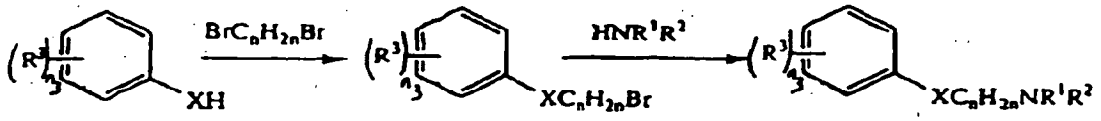
- $-NR^1R^2$ is a pyrrolidinyl group, C_nH_{2n} is a linear chain $-(CH_2)_n-$ and n_3 is zero, X being an oxygen atom with n ranging from 3 to 5, or X being a sulfur atom with n being 4 or 5;
- $-NR^1R^2$ is a piperidinyl group, C_nH_{2n} is a linear chain $-(CH_2)_n-$ and X is an oxygen atom, n_3 being zero with n being 2, 5 or 8 or n_3 being 1 with R^3 being 4-CN and n being 5;
- $-NR^1R^2$ is a diethylamine group, X is an oxygen atom, C_nH_{2n} is a linear chain $-(CH_2)_n-$ and n_3 is 1, R^3 being 4-NO_2 or 4-$COCH_3$ with n being 3 or R^3 being 4-CN with n being 2 to 4;
- $-NR^1R^2$ is a dimethylamine group, X is an oxygen atom, C_nH_{2n} is a linear chain $-(CH_2)_n-$ and n^3 is 1, R^3 being 4-CN with n being 3,

are known in the art.

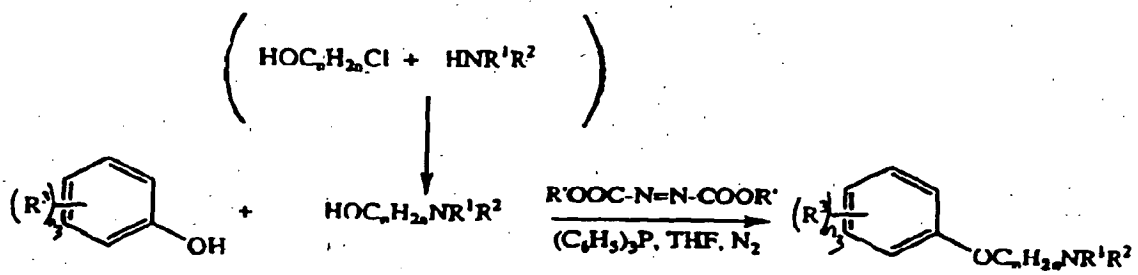
[0038] A subject of the invention is thus the use of these compounds as antagonists at the histamine H_3-receptors, in particular to prepare medicaments acting as H_3-antagonists intended for the treatments detailed below.

[0039] The compounds according to the invention may be prepared according to one of the following schemes 1-5:

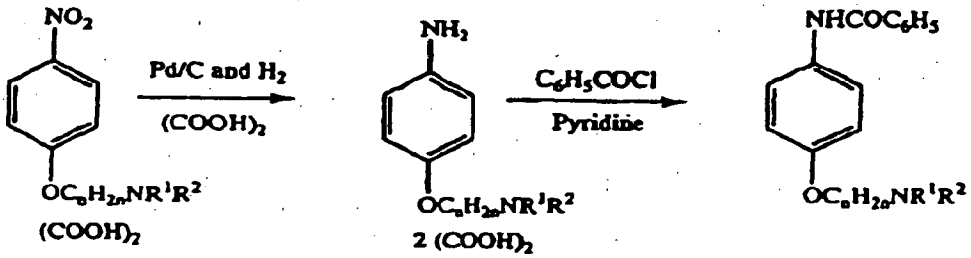
SCHEME 1 (methods A, B, C, D, H and K):



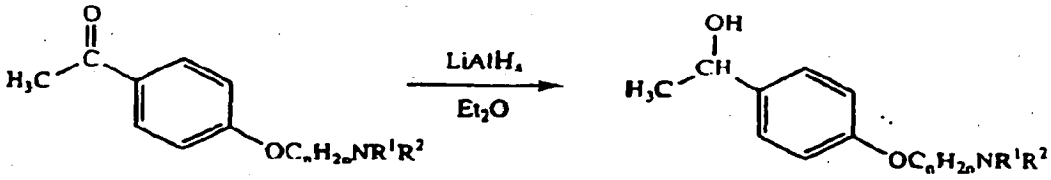
SCHEME 2 (methods F and L):



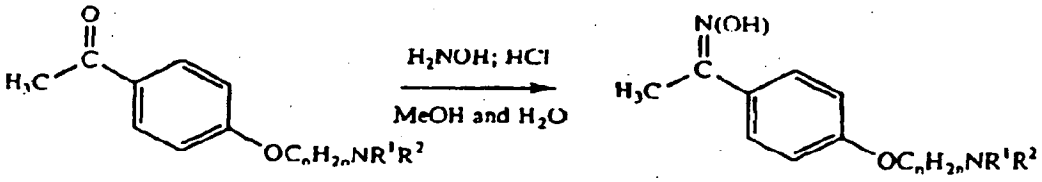
SCHEME 3 (method E):



SCHEME 4 (method G):



SCHEME 5 (method J):



[0040] In these schemes, R^1, R^2, R^3, X and n are as defined in general formula (I).

[0041] Me and Et are intended to mean methyl and ethyl.

[0042] Detailed synthesis procedures are given in the examples.

[0043] The compounds of formula (I) according to the invention have antagonistic properties at the histamine H_3-receptors. They cause an increase in synthesis and release of cerebral histamine.

[0044] This property makes the compounds of the invention useful derivatives in human or veterinary medicine.

[0045] Their therapeutical applications are those known for H_3-antagonist compounds and especially relate to the central nervous system disorders such as Alzheimer disease, mood and attention alterations, cognitive deficits in psychiatric pathologies, obesity, vertigo and motion sickness.

[0046] Therefore, the compounds of formula (I) according to the invention are advantageously used as active ingredient of medicaments which act as an antagonist of H_3-receptors of histamine, in particular of medicaments having psychotropic effects, promoting wakefullness, attention, memory and improving mood, in treatment of pathologies such as Alzheimer disease and other cognitive disorders in aged persons, depressive or simply asthenic states.

[0047] Their nootropic effects can be useful to stimulate attention and memorization capacity in healthy humans.

[0048] In addition, these agents can be useful in treatment of obesity, vertigo and motion sickness.

[0049] It can also be useful to associate the compounds of the invention with other psychiatric agents such as neuroleptics to increase their efficiency and reduce their side effects.

[0050] Application in certain form of epilepsy is also foreseen.

[0051] Their therapeutic applications involve also peripheral organs mainly a stimulant of secretions or gastro-intestinal motricity.

[0052] The compounds of the invention are particularly useful for the treatment of CNS disorders of aged persons.

[0053] The present invention also relates to medicaments having the above-mentioned effects comprising as active ingredient, a therapeutically effective amount of a compound of formula (I).

[0054] The present invention also relates to pharmaceutical compositions containing as active ingredient, a therapeutically effective amount of a compound (I) together with a pharmaceutically acceptable vehicle or excipient.

[0055] The medicaments or pharmaceutical compositions according to the invention can be administered via oral, parenteral or topical routes, the active ingredient being combined with a therapeutically suitable excipient or vehicle.

[0056] According to the invention, oral administration is advantageously used.

[0057] Another subject of the present invention is the use of the compounds of formula (I) for the preparation of H_3-antagonist medicaments according to the above-mentioned forms.

[0058] The invention further relates to the use of the compounds of formula (I) for preparing medicaments having the pre-cited effects.

[0059] Still another subject of the invention is a method for the treatment of precited ailments comprising administering a therapeutically effective dose of a compound (I), optionally in combination with a therapeutically acceptable vehicle or excipient.

[0060] For each of the above-indications, the amount of the active ingredient will depend upon the condition of the patient.

[0061] However, a suitable effective dose will be in general in the range of from 10 to 500 mg per day and of from 1 to 10 mg/day for particularly active compounds.

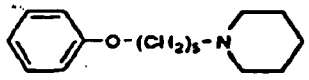
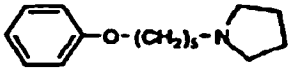
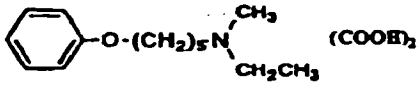
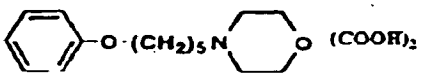
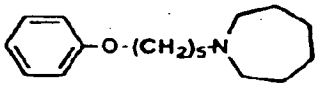
[0062] These doses are given on the basis of the compound and should be adapted for the salts, hydrates or hydrated salts thereof.

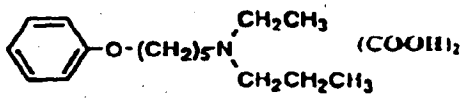
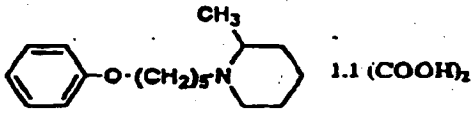
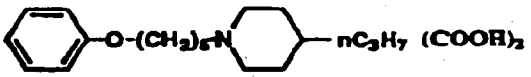
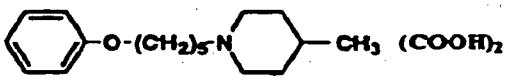
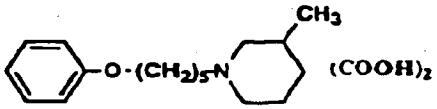
[0063] The invention is now illustrated by the following examples.

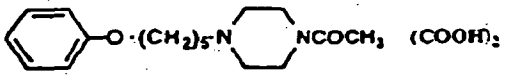
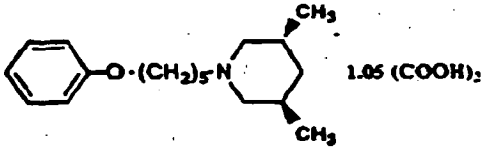
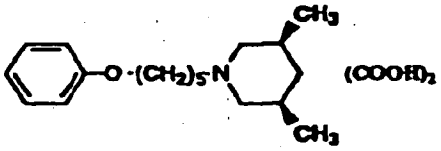
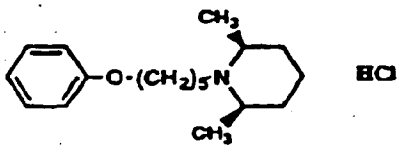
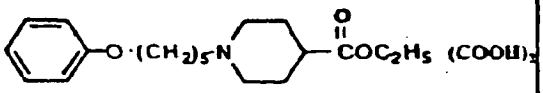
EXAMPLES

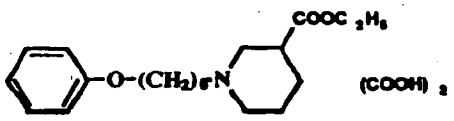
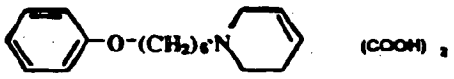
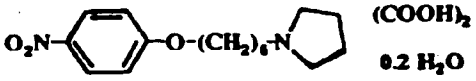
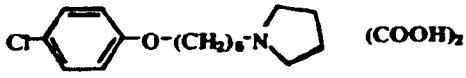
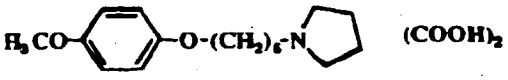
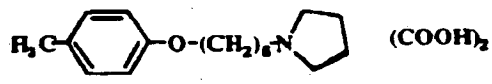
[0064] The structure of the synthesized compounds and their method of preparation as well as their melting point, recrystalisation solvant and elemental analysis are summarized in the following Table I:

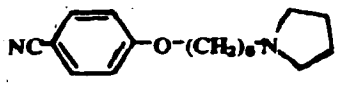
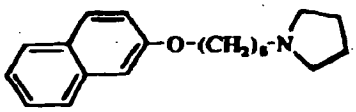
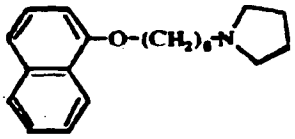
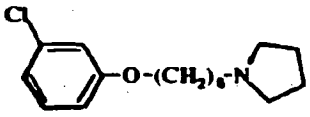
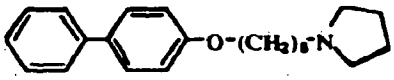
TABLE I:

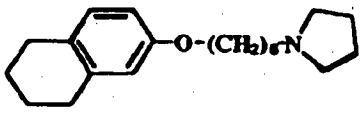
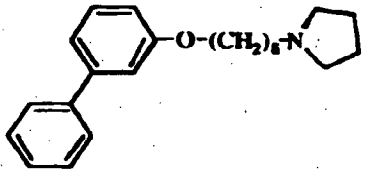
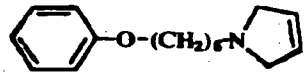
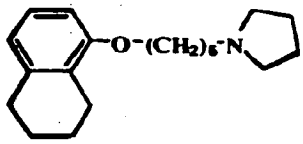
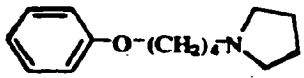
N°	FORMULA STRUCTURE NAME	mp (recryst. solv)	analysis (calc.)	method
1	$C_{16}H_{25}NO; C_2H_2O_4$  1-(5-phenoxypentyl)-piperidine hydrogen oxalate	143-145°C (absolute ethanol)	C: 64.06 (64.07) H: 8.09 (8.16) N: 4.14 (4.15)	A
2	$C_{15}H_{23}NO; C_2H_2O_4$  1-(5-phenoxypentyl)-pyrrolidine hydrogen oxalate	153-155°C (absolute ethanol)	C: 63.06 (63.14) H: 7.78 (7.79) N: 4.42 (4.33)	A
3	$C_{14}H_{23}NO; C_2H_2O_4$  N-methyl-N-(5-phenoxypentyl)-ethylamine hydrogen oxalate	122-124°C (absolute ethanol)	C: 61.74 (61.72) H: 8.24 (8.09) N: 4.52 (4.50)	A
4	$C_{15}H_{23}NO_2; C_2H_2O_4$  1-(5-phenoxypentyl)-morpholine hydrogen oxalate	166-168°C (absolute ethanol)	C: 60.10 (60.16) H: 7.45 (7.31) N: 4.08 (4.13)	A
5	$C_{17}H_{27}NO; C_2H_2O_4$  N-(5-phenoxypentyl)-hexamethyleneimine hydrogen oxalate	132-134°C (absolute ethanol)	C: 64.70 (64.93) H: 8.34 (8.32) N: 3.85 (3.99)	A

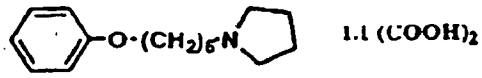
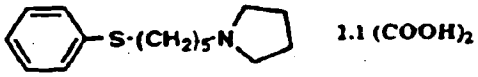
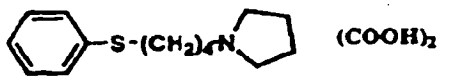
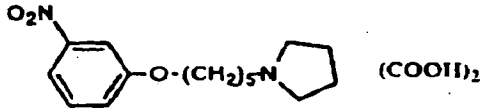
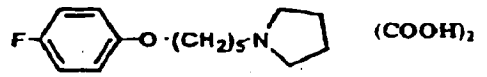
6	$C_{16}H_{27}NO; C_2H_2O_4$  N-ethyl-N-(5-phenoxypentyl)-propylamine hydrogen oxalate	90-91°C (isopropyl alcohol)	C: 63.60 (63.69) H: 8.81 (8.61) N: 3.97 (4.13)	B
7	$C_{17}H_{27}NO; 1.1\ C_2H_2O_4$  1-(5-phenoxypentyl)-2-methyl-piperidine hydrogen oxalate	80-83°C (isopropyl alcohol)	C: 64.15 (63.98) H: 8.42 (8.17) N: 3.97 (3.89)	B
8	$C_{19}H_{31}NO; C_2H_2O_4$  1-(5-phenoxypentyl)-4-propyl-piperidine hydrogen oxalate	165-166°C (absolute ethanol)	C: 66.27 (66.46) H: 8.94 (8.76) N: 3.72 (3.69)	B
9	$C_{17}H_{27}NO; C_2H_2O_4$  1-(5-phenoxypentyl)-4-methyl-piperidine hydrogen oxalate	151-152°C (absolute ethanol)	C: 64.87 (64.93) H: 8.41 (8.32) N: 4.01 (3.99)	B
10	$C_{17}H_{27}NO; C_2H_2O_4$  1-(5-phenoxypentyl)-3-methyl-piperidine hydrogen oxalate	140-141°C (isopropyl alcohol)	C: 65.35 (64.93) H: 8.49 (8.32) N: 4.00 (3.99)	B

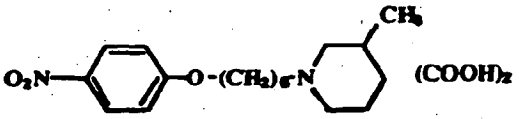
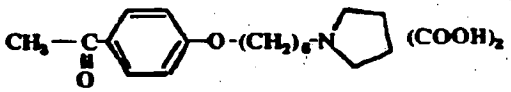
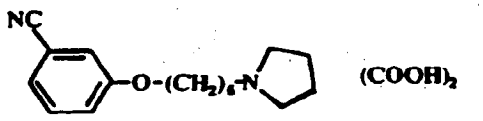
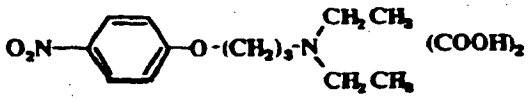
11	$C_{17}H_{25}N_2O_2$; $C_2H_2O_4$  1-acetyl-4-(5-phenoxypentyl)-piperazine hydrogen oxalate	186-188°C (absolute ethanol)	C: 59.78 (59.99) H: 7.47 (7.42) N: 7.35 (7.36)	B
12	$C_{18}H_{29}NO$; 1.05 $C_2H_2O_4$  1-(5-phenoxypentyl)-3,5-trans-dimethyl-piperidine hydrogen oxalate	154-155°C (absolute ethanol)	C: 65.16 (65.25) H: 8.61 (8.47) N: 3.66 (3.79)	B
13	$C_{18}H_{29}NO$; $C_2H_2O_4$  1-(5-phenoxypentyl)-3,5-cis-dimethyl-piperidine hydrogen oxalate	154-155°C (isopropyl alcohol)	C: 65.62 (65.73) H: 8.64 (8.55) N: 3.63 (3.83)	B
14	$C_{18}H_{29}NO$; HCl  1-(5-phenoxypentyl)-2,6-cis-dimethyl-piperidine hydrochloride	135-136°C (acetone)	C: 69.18 (69.32) H: 9.79 (9.70) N: 4.28 (4.49)	B
15	$C_{19}H_{29}NO_3$; $C_2H_2O_4$  4-carboethoxy-1-(5-phenoxypentyl)-piperidine hydrogen oxalate	149-150°C (absolute ethanol)	C: 61.16 (61.60) H: 7.76 (7.63) N: 3.40 (3.42)	B

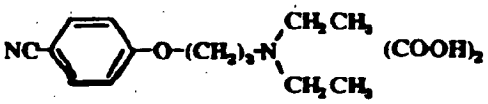
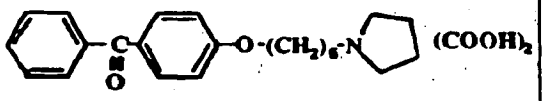
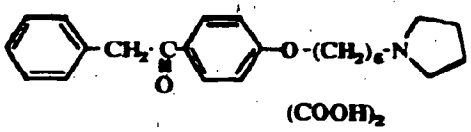
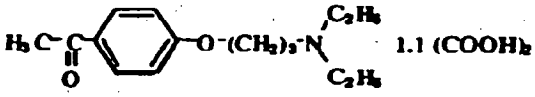
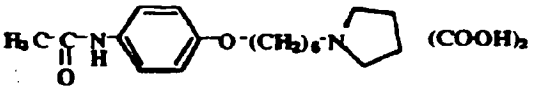
16	$C_{19}H_{29}NO_3$; $C_2H_2O_4$  3-carboethoxy-1-(5-phenoxypentyl)-piperidine hydrogen oxalate	117-118°C (isopropyl alcohol)	C: 61.54 (61.60) H: 7.87 (7.63) N: 3.29 (3.42)	B
17	$C_{16}H_{23}NO$; $C_2H_2O_4$  1-(5-phenoxypentyl)-1,2,3,6-tetrahydropyridine hydrogen oxalate	177-179°C (methanol)	C: 64.19 (64.46) H: 7.49 (7.51) N: 4.25 (4.18)	B
18	$C_{15}H_{22}N_2O_3$; $C_2H_2O_4$; 0.2 H_2O  1-[5-(4-nitrophenoxy)-pentyl]-pyrrolidine hydrogen oxalate	145-147°C (absolute ethanol)	C: 54.89 (54.89) H: 6.68 (6.61) N: 7.41 (7.53)	C
19	$C_{15}H_{22}ClNO$; $C_2H_2O_4$  1-[5-(4-chlorophenoxy)-pentyl]-pyrrolidine hydrogen oxalate	139-141°C (absolute ethanol)	C: 57.00 (57.06) H: 6.63 (6.76) N: 3.79 (3.91) Cl: 10.24 (9.91)	C
20	$C_{16}H_{25}NO_2$; $C_2H_2O_4$  1-[5-(4-methoxyphenoxy)-pentyl]-pyrrolidine hydrogen oxalate	115-116°C (absolute ethanol)	C: 61.22 (61.17) H: 7.72 (7.70) N: 4.03 (3.96)	C
21	$C_{16}H_{25}NO$; $C_2H_2O_4$  1-[5-(4-methylphenoxy)-pentyl]-pyrrolidine hydrogen oxalate	138-140°C (absolute ethanol)	C: 64.05 (64.07) H: 8.00 (8.07) N: 4.10 (4.15)	C

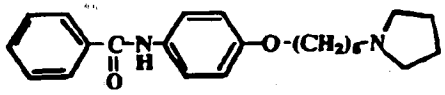
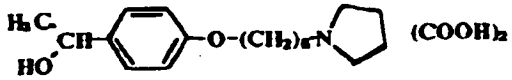
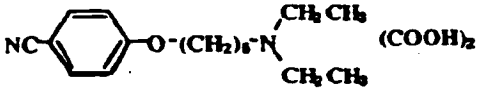
22	$C_{16}H_{22}N_2O$; 1.1 $C_2H_2O_4$  1.1 $(COOH)_2$ 1-[5-(4-cyanophenoxy)-pentyl]-pyrrolidine hydrogen oxalate	129-130°C (absolute ethanol)	C: 61.24 (61.16) H: 6.81 (6.82) N: 7.95 (7.84)	C
23	$C_{19}H_{25}NO$; $C_2H_2O_4$  $(COOH)_2$ 1-[5-(2-naphthyloxy)-pentyl]-pyrrolidine hydrogen oxalate	166-167°C (methanol)	C: 67.42 (67.54) H: 7.26 (7.29) N: 3.66 (3.75)	C
24	$C_{19}H_{25}NO$; 1.25 $C_2H_2O_4$  1.25 $(COOH)_2$ 1-[5-(1-naphthyloxy)-pentyl]-pyrrolidine hydrogen oxalate	160-163°C (methanol)	C: 65.12 (65.22) H: 7.17 (7.00) N: 3.52 (3.54)	C
25	$C_{15}H_{22}ClNO$; $C_2H_2O_4$  $(COOH)_2$ 1-[5-(3-chlorophenoxy)-pentyl]-pyrrolidine hydrogen oxalate	131-132°C (absolute ethanol)	C: 56.94 (57.06) H: 6.67 (6.76) N: 3.74 (3.91) Cl: 9.64 (9.91)	C
26	$C_{21}H_{27}NO$; $C_2H_2O_4$  $(COOH)_2$ 1-[5-(4-phenylphenoxy)-pentyl]-pyrrolidine hydrogen oxalate	189-190°C (methanol)	C: 69.16 (69.15) H: 7.39 (7.32) N: 3.39 (3.51)	C

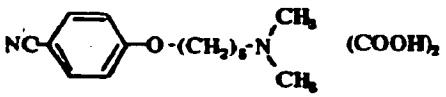
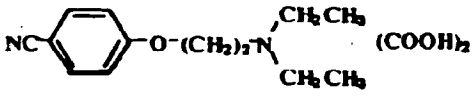
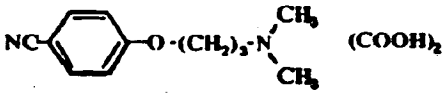
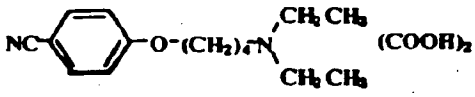
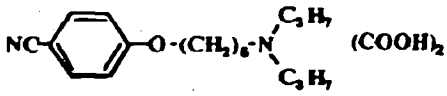
27	$C_{19}H_{29}NO$; $C_2H_2O_4$  $(COOH)_2$ 1-{5-[2-(5,6,7,8-tetrahydronaphthyl)-oxy]-pentyl}-pyrrolidine hydrogen oxalate	131-132°C (absolute ethanol)	C: 66.73 (66.82) H: 8.37 (8.28) N: 3.68 (3.71)	C
28	$C_{21}H_{27}NO$; 1.1 $C_2H_2O_4$  1.1 $(COOH)_2$ 1-[5-(3-phenylphenoxy)-pentyl]-pyrrolidine hydrogen oxalate	155-157°C (absolute ethanol)	C: 68.40 (68.22) H: 7.04 (7.21) N: 3.45 (3.43)	C
29	$C_{15}H_{21}NO$; $C_2H_2O_4$  $(COOH)_2$ 1-(5-phenoxypentyl)-2,5-dihydropyrrole hydrogen oxalate	140-141°C (absolute ethanol)	C: 63.45 (63.54) H: 7.26 (7.21) N: 4.26 (4.36)	B
30	$C_{19}H_{29}NO$; $C_2H_2O_4$  $(COOH)_2$ 1-{5-[1-(5,6,7,8-tetrahydronaphthyl)-oxy]-pentyl}-pyrrolidine hydrogen oxalate	148-149°C (absolute ethanol)	C: 66.99 (66.82) H: 8.47 (8.28) N: 3.72 (3.71)	C
31	$C_{14}H_{21}NO$; $C_2H_2O_4$  $(COOH)_2$ 1-(4-phenoxybutyl)-pyrrolidine hydrogen oxalate	143-144°C (absolute ethanol)	C: 62.25 (62.12) H: 7.46 (7.49) N: 4.49 (4.53)	C

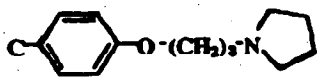
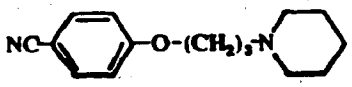
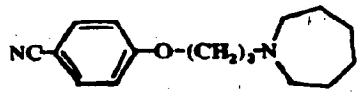
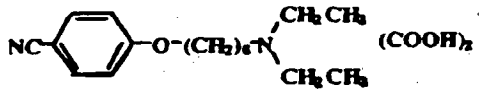
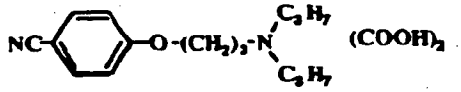
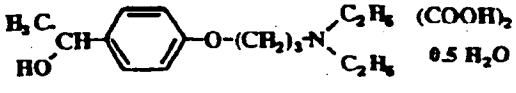
32	$C_{16}H_{25}NO$; 1.1 $C_2H_2O_4$  1.1 $(COOH)_2$ 1-(6-phenoxyhexyl)-pyrrolidine hydrogen oxalate	146-147°C (absolute ethanol)	C: 63.06 (63.10) H: 8.03 (7.91) N: 4.32 (4.04)	C
33	$C_{15}H_{23}NS$; 1.1 $C_2H_2O_4$  1.1 $(COOH)_2$ 1-(5-phenylthiopentyl)-pyrrolidine hydrogen oxalate	150-152°C (absolute ethanol)	C: 59.52 (59.29) H: 7.44 (7.29) N: 4.06 (4.02)	C
34	$C_{14}H_{21}NS$; $C_2H_2O_4$  $(COOH)_2$ 1-(4-phenylthiobutyl)-pyrrolidine hydrogen oxalate	114-116°C (absolute ethanol)	C: 59.24 (59.05) H: 7.16 (7.12) N: 4.16 (4.30) S: 9.79 (9.85)	C
35	$C_{13}H_{19}NO$; $C_2H_2O_4$  $(COOH)_2$ 1-(3-phenoxypropyl)-pyrrolidine hydrogen oxalate	169-170°C (absolute ethanol)	C: 60.98 (61.00) H: 7.14 (7.17) N: 4.64 (4.74)	C
36	$C_{15}H_{22}N_2O_3$; $C_2H_2O_4$  $(COOH)_2$ 1-[5-(3-nitrophenoxy)-pentyl]-pyrrolidine hydrogen oxalate	130-131°C (absolute ethanol)	C: 55.30 (55.43) H: 6.55 (6.57) N: 7.49 (7.60)	C
37	$C_{15}H_{22}FNO$; $C_2H_2O_4$  $(COOH)_2$ 1-[5-(4-fluorophenoxy)-pentyl]-pyrrolidine hydrogen oxalate	149-150°C (absolute ethanol)	C: 59.52 (59.81) H: 7.12 (7.09) N: 4.05 (4.10)	C

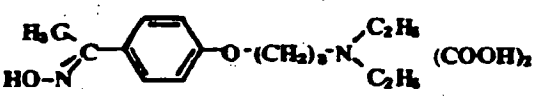
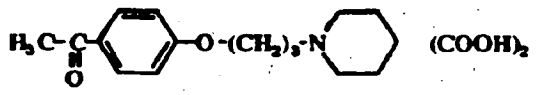
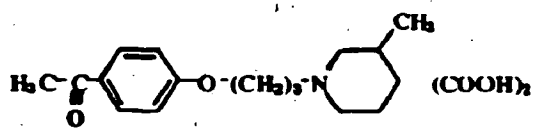
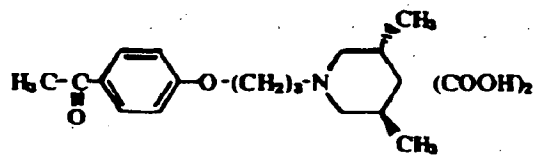
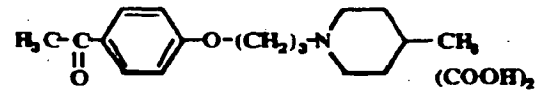
38	$C_{17}H_{26}N_2O_3$; $C_2H_2O_4$  1-[5-(4-nitrophenoxy)-pentyl]-3-methyl-piperidine hydrogen oxalate	148-149°C (absolute ethanol)	C: 57.32 (57.55) H: 7.19 (7.12) N: 6.89 (7.07)	C
39	$C_{17}H_{25}NO_2$; $C_2H_2O_4$  1-[5-(4-acetylphenoxy)-pentyl]-pyrrolidine hydrogen oxalate	130-134°C (absolute ethanol)	C: 62.43 (62.45) H: 7.41 (7.45) N: 3.75 (3.83)	D
40	$C_{15}H_{24}N_2O$, 2.1 $C_2H_2O_4$  1-[5-(4-aminophenoxy)-pentyl]-pyrrolidine di-(hydrogen oxalate)	120-122°C (absolute ethanol)	C: 52.49 (52.72) H: 6.74 (6.50) N: 6.32 (6.40)	E_1
41	$C_{16}H_{22}N_2O$; $C_2H_2O_4$  1-[5-(3-cyanophenoxy)-pentyl]-pyrrolidine hydrogen oxalate	119-120°C (absolute ethanol)	C: 61.95 (62.05) H: 6.88 (6.94) N: 8.00 (8.04)	C
42	$C_{13}H_{20}N_2O_3$; $C_2H_2O_4$  N-[3-(4-nitrophenoxy)-propyl]-diethylamine hydrogen oxalate	160-161°C (absolute ethanol/ methanol 1:1)	C: 52.46 (52.63) H: 6.49 (6.48) N: 8.10 (8.12)	F

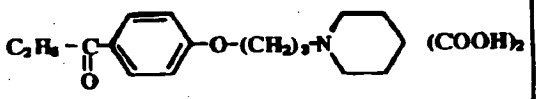
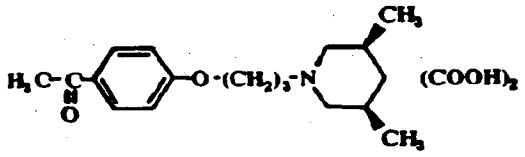
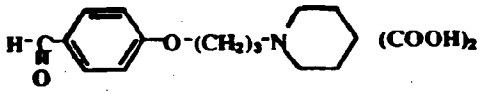
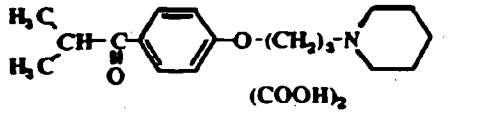
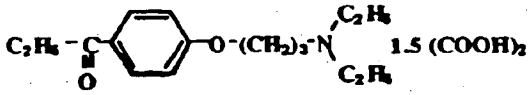
43	$C_{14}H_{20}N_2O$; $C_2H_2O_4$  N-[3-(4-cyanophenoxy)-propyl]-diethylamine hydrogen oxalate	148-150°C (absolute ethanol)	C: 59.40 (59.62) H: 6.82 (6.88) N: 8.60 (8.69)	F
44	$C_{22}H_{27}NO_2$; $C_2H_2O_4$  1-[5-(4-benzoylphenoxy)-pentyl]-pyrrolidine hydrogen oxalate	141-142°C (absolute ethanol)	C: 67.17 (67.43) H: 6.80 (6.84) N: 3.18 (3.28)	D
45	$C_{23}H_{29}NO_2$; $C_2H_2O_4$  1-{5-[4-(phenylacetyl)-phenoxy]-pentyl}-pyrrolidine hydrogen oxalate	177-178°C (absolute ethanol)	C: 67.77 (68.01) H: 7.09 (7.08) N: 3.26 (3.17)	D
46	$C_{15}H_{23}NO_2$; 1.1 $C_2H_2O_4$  N-[3-(4-acetylphenoxy)-propyl]-diethylamine hydrogen oxalate	108-110°C (absolute ethanol)	C: 59.30 (59.30) H: 7.47 (7.29) N: 4.18 (4.02)	F
47	$C_{17}H_{26}N_2O_2$; $C_2H_2O_4$  1-[5-(4-acetamidophenoxy)-pentyl]-pyrrolidine hydrogen oxalate	142-144°C (absolute ethanol)	C: 59.67 (59.99) H: 7.55 (7.42) N: 7.25 (7.36)	C

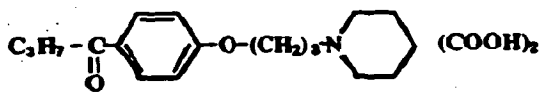
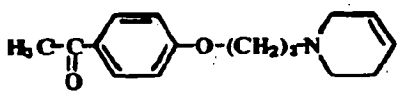
48	$C_{21}H_{27}NO_2$; $C_2H_2O_4$  1-[5-(4-phenoxyphenoxy)-pentyl]-pyrrolidine hydrogen oxalate	135-136°C (absolute ethanol)	C: 66.49 (66.49) H: 7.05 (7.04) N: 3.24 (3.37)	D
49	$C_{22}H_{28}N_2O_2$; 1.1 $C_2H_2O_4$  1.1 $(COOH)_2$ 1-[5-(4-N-benzamidophenoxy)-pentyl]-pyrrolidine hydrogen oxalate	176-178°C (absolute ethanol)	C: 64.56 (64.38) H: 6.89 (6.74) N: 6.26 (6.20)	E_2
50	$C_{17}H_{27}NO_2$; $C_2H_2O_4$  1-{5-[4-(1-hydroxyethyl)-phenoxy]-pentyl}-pyrrolidine hydrogen oxalate	102-104°C (absolute ethanol)	C: 61.89 (62.11) H: 7.94 (7.96) N: 3.77 (3.81)	G
51	$C_{16}H_{24}N_2O$; $C_2H_2O_4$  N-[5-(4-cyanophenoxy)-pentyl]-diethylamine hydrogen oxalate	120-122°C (absolute ethanol)	C: 61.56 (61.70) H: 7.54 (7.48) N: 7.87 (7.99)	H
52	$C_{17}H_{24}N_2O$; $C_2H_2O_4$  1-[5-(4-cyanophenoxy)-pentyl]-piperidine hydrogen oxalate	115-116°C (absolute ethanol)	C: 62.62 (62.97) H: 7.20 (7.23) N: 7.76 (7.73)	H

53	$C_{14}H_{20}N_2O$; $C_2H_2O_4$  N-[5-(4-cyanophenoxy)-pentyl]-dimethylamine hydrogen oxalate	148-149°C (absolute ethanol)	C: 59.68 (59.62) H: 6.76 (6.88) N: 8.57 (8.69)	H
54	$C_{13}H_{18}N_2O$; $C_2H_2O_4$  N-[2-(4-cyanophenoxy)-ethyl]-diethylamine hydrogen oxalate	124-125°C (absolute ethanol)	C: 58.15 (58.43) H: 6.30 (6.54) N: 8.95 (9.09)	H.
55	$C_{12}H_{16}N_2O$; $C_2H_2O_4$  N-[3-(4-cyanophenoxy)-propyl]-dimethylamine hydrogen oxalate	166-167°C (absolute ethanol/ methanol 1:1)	C: 57.01 (57.14) H: 6.02 (6.16) N: 9.46 (9.52)	H
56	$C_{15}H_{22}N_2O$; $C_2H_2O_4$  N-[4-(4-cyanophenoxy)-butyl]-diethylamine hydrogen oxalate	143-145°C (absolute ethanol)	C: 60.80 (60.70) H: 7.11 (7.19) N: 8.22 (8.33)	H
57	$C_{18}H_{28}N_2O$; $C_2H_2O_4$  N-[5-(4-cyanophenoxy)-pentyl]-dipropylamine hydrogen oxalate	134-136°C (absolute ethanol)	C: 63.38 (63.47) H: 8.11 (7.99) N: 7.29 (7.40)	H

58	$C_{14}H_{18}N_2O$; 1.1 $C_2H_2O_4$  1.1 $(COOH)_2$ 1-[3-(4-cyanophenoxy)-propyl]-pyrrolidine hydrogen oxalate	163-165°C (absolute ethanol)	C: 58.95 (59.08) H: 6.23 (6.18) N: 8.43 (8.51)	H
59	$C_{15}H_{20}N_2O$; 1.05 $C_2H_2O_4$  1.05 $(COOH)_2$ 1-[3-(4-cyanophenoxy)-propyl]-piperidine hydrogen oxalate	151-153°C (absolute ethanol)	C: 60.62 (60.61) H: 6.66 (6.57) N: 8.25 (8.27)	H
60	$C_{16}H_{22}N_2O$; 1.05 $C_2H_2O_4$  1.05 $(COOH)_2$ N-[3-(4-cyanophenoxy)-propyl]-hexamethyleneimine hydrogen oxalate	124-125°C (absolute ethanol)	C: 61.62 (61.60) H: 6.94 (6.88) N: 7.87 (7.94)	H
61	$C_{17}H_{26}N_2O$; $C_2H_2O_4$  $(COOH)_2$ N-[6-(4-cyanophenoxy)-hexyl]-diethylamine hydrogen oxalate	110-112°C (absolute ethanol)	C: 62.90 (62.62) H: 7.76 (7.74) N: 7.61 (7.69)	H
62	$C_{16}H_{24}N_2O$; $C_2H_2O_4$  $(COOH)_2$ N-[3-(4-cyanophenoxy)-propyl]-dipropylamine hydrogen oxalate	127-128°C (absolute ethanol)	C: 61.57 (61.70) H: 7.57 (7.48) N: 7.91 (7.99)	H
63	$C_{15}H_{25}NO_2$; $C_2H_2O_4$; 0.5 H_2O  $(COOH)_2$ 0.5 H_2O N-3-[4-(1-hydroxyethyl)-phenoxy]-propyl-diethylamine hydrogen oxalate hemihydrate	33-36°C (isopropyl alcohol)	C: 58.15 (58.27) H: 8.15 (8.05) N: 4.21 (4.00)	G

64	$C_{15}H_{24}N_2O_2$; $C_2H_2O_4$  4'-(3-diethylaminopropoxy)-acetophenone-oxime hydrogen oxalate	99-100°C (absolute ethanol)	C: 57.26 (57.61) H: 7.47 (7.39) N: 7.72 (7.90)	J
65	$C_{16}H_{23}NO_2$; $C_2H_2O_4$  1-[3-(4-acetylphenoxy)-propyl]-piperidine hydrogen oxalate	159-160°C (absolute ethanol)	C: 61.18 (61.52) H: 7.11 (7.17) N: 3.96 (3.99)	K
66	$C_{17}H_{25}NO_2$; $C_2H_2O_4$  1-[3-(4-acetylphenoxy)-propyl]-3-methyl-piperidine hydrogen oxalate	143-144°C (absolute ethanol)	C: 62.11 (62.45) H: 7.41 (7.45) N: 3.79 (3.83)	K
67	$C_{18}H_{27}NO_2$; $C_2H_2O_4$  1-[3-(4-acetylphenoxy)-propyl]-3,5-trans-dimethyl-piperidine hydrogen oxalate	171-172°C (absolute ethanol)	C: 63.06 (63.31) H: 7.44 (7.70) N: 3.64 (3.69)	K
68	$C_{17}H_{25}NO_2$; $C_2H_2O_4$  1-[3-(4-acetylphenoxy)-propyl]-4-methyl-piperidine hydrogen oxalate	160-161°C (absolute ethanol)	C: 62.47 (62.45) H: 7.46 (7.45) N: 3.77 (3.83)	K

69	$C_{17}H_{25}NO_2$; $C_2H_2O_4$  1-[3-(4-propionylphenoxy)-propyl]-piperidine hydrogen oxalate	148-149°C (absolute ethanol)	C: 62.54 (62.45) H: 7.51 (7.45) N: 3.79 (3.83)	L
70	$C_{18}H_{27}NO_2$; $C_2H_2O_4$  1-[3-(4-acetylphenoxy)-propyl]-3,5-cis-dimethyl-piperidine hydrogen oxalate	174-175°C (absolute ethanol)	C: 63.22 (63.31) H: 7.60 (7.70) N: 3.64 (3.69)	K
71	$C_{15}H_{21}NO_2$; $C_2H_2O_4$  1-[3-(4-formylphenoxy)-propyl]-piperidine hydrogen oxalate	152-153°C (absolute ethanol)	C: 60.23 (60.52) H: 6.81 (6.87) N: 4.15 (4.15)	L
72	$C_{18}H_{27}NO_2$; $C_2H_2O_4$  1-[3-(4-isobutyrylphenoxy)-propyl]-piperidine hydrogen oxalate	121-122°C (absolute ethanol)	C: 63.02 (63.31) H: 7.73 (7.70) N: 3.66 (3.69)	L
73	$C_{16}H_{25}NO_2$; 1.5 $C_2H_2O_4$  N-[3-(4-propionylphenoxy)-propyl]-diethylamine hydrogen oxalate	118-120°C (absolute ethanol)	C: 57.27 (57.28) H: 7.00 (7.08) N: 3.47 (3.52)	L

74	$C_{18}H_{27}NO_2$; $C_2H_2O_4$  1-[3-(4-butyrylphenoxy)-propyl]-piperidine hydrogen oxalate	138-139°C (absolute ethanol)	C: 63.09 (63.31) H: 7.78 (7.70) N: 3.75 (3.69)	L
75	$C_{16}H_{21}NO_2$; 1.1 $C_2H_2O_4$  1.1 $(COOH)_2$ 1-[3-(4-acetylphenoxy)-propyl]-1,2,3,6-tetrahydropyridine hydrogen oxalate	143-144°C (absolute ethanol)	C: 61.21 (61.00) H: 6.25 (6.52) N: 4.00 (3.91)	K

[0065] Compounds 1 to 75 are prepared according to the following procedures:

METHOD A:

[0066] A solution of 1-bromo-5-phenoxypentane (1.4 to 3.5 mmol) in ten equivalents of the suitable secondary amine was heated to reflux temperature with stirring for 48 hours (compds. 1, 3 and 4), 24 hours (compd. 2) or 4 hours (compd. 5). After cooling, the excess base was removed under reduced pressure and the residue diluted with aqueous sodium hydroxide. The product was extracted with diethyl ether, the organic extracts washed with water, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The remaining oil was converted to oxalate salt by dissolving in a small amount of absolute ethanol and adding a solution of two equivalents oxalic acid in absolute ethanol. The precipitate formed was washed with diethyl ether and recrystallised from absolute ethanol.

METHOD B:

[0067] A solution of 1-bromo-5-phenoxypentane (0.9 to 1.7 mmol) and an excess of the suitable secondary amine (2.3 to 10 equivalents) in 10 ml absolute ethanol was heated to reflux temperature with stirring for 48 hours (compd. 6) or 24 hours (compds. 7, 8, 9, 10, 11, 12&13, 14, 15, 16, 17 and 29). After cooling, the solvent was removed under reduced pressure and the residue diluted with aqueous sodium hydroxide. The product was extracted with diethyl ether, the organic extracts washed with water, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The cis and trans isomers 12 and 13 were separated by column chromatography on silica gel eluting with a solvent mixture of petroleum spirit (bp 60-80°C), diethyl ether and triethylamine in the ratio 66:33:1, and the eluent was removed under reduced pressure to leave an oil. Compounds 14 and 16 were purified by column chromatography on silica gel eluting with diethyl ether and triethylamine in the ratio 99:1, and the eluent was removed under reduced pressure to leave an oil. The oil was converted to oxalate salt (compds. 6, 7, 8, 9, 11, 12, 13, 15, 16, 17 and 29) by dissolving in a small amount of absolute ethanol and adding a solution of two equivalents of oxalic acid in absolute ethanol. If no precipitate appeared, diethyl ether was added to form a precipitate. The solid was washed with diethyl ether and recrystallised from isopropyl alcohol (compds. 6, 7, 10, 13 and 16), absolute ethanol (compds. 8, 9, 11, 12, 15 and 29) or methanol (compd. 17). The oil was converted to hydrochloride salt (compd. 14) by adding 2N HCl. The precipitate was formed in a mixture of chloroform and diethyl ether (1:1) and recrystallised from acetone.

METHOD C:

[0068] A solution of the suitable α-bromo-ω-aryloxy alkane (0.4 to 1.4 mmol) or ω-bromoalkyl phenyl sulphide (1 mmol, compds. 33 and 34) and an exc ss of pyrrolidine (10 to 15 equivalents) or 3-methylpiperidine (10 equivalents,

compd. 38) in 10 ml absolute ethanol was heated to reflux temperature with stirring for 24 hours or 16 hours (compd. 47). After cooling, the solvent was removed under reduced pressure and the residue diluted with aqueous sodium hydroxide. The product was extracted with diethyl ether, the organic extracts washed with water, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The remaining oil was converted to oxalate salt by dissolving in a small amount of absolute ethanol and adding a solution of two equivalents oxalic acid in absolute ethanol. If no precipitate appeared, diethyl ether was added to form a precipitate. The solid was washed with diethyl ether and recrystallised from absolute ethanol.

METHOD D:

[0069] A solution of the suitable 4'-(5-bromopentoxy)phenyl ketone (0.7 to 1 mmol, compds. 39, 44 and 45) or 1-bromo, 5-(4-phenoxyphenoxy)pentane (0.6 mmol, compd. 48) and an excess of pyrrolidine (10 to 15 equivalents) in 10 ml absolute ethanol was heated to reflux temperature with stirring for 16 hours (compds. 39, 44 and 48) or 24 hours (compd. 45). After cooling, the solvent was removed under reduced pressure and the residue diluted with aqueous sodium hydroxide. The product was extracted with chloroform (compds. 39, 45 and 48) or dichloromethane (compd. 44), the organic extracts dried over magnesium sulphate, filtered and concentrated under reduced pressure. The r maining oil was converted to oxalate salt by dissolving in a small amount of absolute ethanol and adding a solution of two equivalents oxalic acid in absolute ethanol. The precipitate was washed with diethyl ether and recrystallised from absolute ethanol (recrystallised twice from absolute ethanol in the case of compd. 39).

METHOD E:

[0070]

1. The oxalate 18 was prepared according to method C. A solution of compound 18 (0.57 mmol) in 10 ml methanol and 10 ml absolute ethanol was placed with 100 mg of palladium (5%) on carbon catalyst in a two-neck round-bottom flask fitted with a balloon filled with hydrogen. The mixture was stirred vigorously at room temperature and the flask was purged of air and filled with hydrogen. After 3 hours, the catalyst was filtered off on celite and the solvent removed under reduced pressure. The residual solid was converted to oxalate salt by dissolving in methanol and adding a solution of oxalic acid (2 equivalents) in absolute ethanol. Diethyl ether was added to form a precipitate. The product was recrystallised from absolute ethanol.
2. To a solution of compound 40 (0.35 mmol) in pyridine vigorously stirred at 0°C was added dropwise a slight excess of benzoyl chloride (0.4 mmol). The stirring was allowed to continue 20 minutes after the end of the addition after which the mixture was placed in the refrigerator overnight (16 hours). The solvent was removed under reduced pressure and the residue diluted with aqueous sodium hydroxide. The product was extracted with chloroform, the organic extracts dried over magnesium sulphate, filtered and concentrated under reduced pressure. The remaining oil was converted to oxalate salt by dissolving in a small amount of absolute ethanol and adding a solution of two equivalents oxalic acid in absolute ethanol. The precipitate was dissolved in methanol, filtered, and concentrated under reduced pressure the solid was recrystallised from absolute ethanol

METHOD F:

[0071] In a three-neck flask kept under nitrogen was placed a solution of the suitable phenol (1.6 mmol), 3-(diethylamino)propanol (1.5 mmol), and triphenyl phosphine (1.9 mmol) in 10 ml freshly distilled tetrahydrofuran. The mixture was stirred and cooled to 0°C with an ice and salt bath. A solution of diisopropyl azodicarboxylate (2 mmol) in 10 ml tetrahydrofuran was added very slowly (typically over 40 minutes) and the mixture was allowed to warm to room temperature after which it was stirred overnight at room temperature (16 hours). The solvent was then removed under reduced pressure, the residue dissolved in ethyl acetate (20 ml) and the product extracted with 2N HCl (2x10 ml). The aqueous solution was neutralised with sodium hydroxide and the product extracted with dichloromethane. After drying over magnesium sulphate and filtration, the solvent was removed under reduced pressure. The residue was converted to oxalate salt by dissolving in a small amount of absolute ethanol and adding a solution of two equivalents oxalic acid in absolute ethanol. If no precipitate appeared, diethyl ether was added to form a precipitate. The solid was washed with diethyl ether and recrystallised from absolute ethanol (compds. 43 and 46) or from a 1:1 mixture of methanol and absolute ethanol (compd. 42).

METHOD G:

[0072] A solution of the free base of compound 39 (0.6 mmol) or compound 46 (0.8 mmol) in 20 ml dry diethyl ether

was added dropwise to a stirred suspension of lithium aluminium hydride (0.6 or 0.8 mmol) in 20 ml dry diethyl ether kept under nitrogen. The mixture was stirred at room temperature under nitrogen for two hours. Ice-cold water was carefully added and the organic layer decanted. The aqueous phase was extracted with diethyl ether. The combined organic solutions were dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a yellow oil. The oil was converted to oxalate salt by dissolving in a small amount of absolute ethanol and adding a solution of two equivalents oxalic add in absolute ethanol. The precipitate was washed with diethyl ether and recrystallised from absolute ethanol (compd 50) or from isopropyl alcohol, giving a very hygroscopic solid (compd. 63).

METHOD H:

[0073] A solution of the suitable α-bromo-ω-(4-cyanophenoxy) alkane (0.5 to 0.7 mmol) and an excess of the suitable secondary amine (8 to 12 equivalents) in 10 ml absolute ethanol was heated to reflux temperature with stirring for 24 hours (compds. 54, 55, 57 and 60), 20 hours (compd. 52), 16 hours (compds. 56, 58, 59 and 61) or 8 hours (compd. 51) or was stirred at room temperature for 48 hours (compd. 53) or 24 hours (compd. 60). After cooling, the solvent was removed under reduced pressure and the residue diluted with aqueous sodium hydroxide. The product was extracted with diethyl ether, the organic extracts washed with water, dried over magnesium sulphate, filtered and concentrated under reduced pressure. Compound 62 was purified by column chromatography on silica gel eluting with ethyl acetate, and concentrated under reduced pressure. For all the compounds of method H, the remaining oil was converted to oxalate salt by dissolving in a small amount of absolute ethanol and adding a solution of two equivalents oxalic acid in absolute ethanol. If no precipitate appeared, diethyl ether was added to form a precipitate. The solid was washed with diethyl ether and recrystallised from absolute ethanol (two recrystallisations were required for compds. 58 and 59) or from a 1:1 mixture of methanol and absolute ethanol (compd. 55).

METHOD J:

[0074] A solution of compound 46 (1 mmol) in 10 ml methanol was stirred at room temperature and a solution of hydroxylamine hydrochloride (2 equivalents) in 2 ml water was added. The mixture was stirred at 50-70°C in a water bath for 20 minutes. Methanol was removed under reduced pressure. The residue diluted with aqueous sodium hydroxide. The product was extracted with diethyl ether, the organic extracts washed with water, dried over magnesium sulphate, filtered and concentrated under reduced pressure. Compound 64 was purified by column chromatography on silica gel eluting with ethyl acetate, and concentrated under reduced pressure. The remaining oil was converted to oxalate salt by dissolving in a small amount of absolute ethanol and adding a solution of two equivalents oxalic acid in absolute ethanol. Diethyl ether was added to form a precipitate. The solid was washed with diethyl ether and recrystallised from absolute ethanol.

METHOD K:

[0075] A solution of 4'-(3-bromopropoxy)acetophenone (0.8 to 1.9 mmol) and an excess of the suitable piperidine (3 to 10 equivalents) in 10 ml absolute ethanol was heated to reflux temperature with stirring for 16 hours. After cooling, the solvent was removed under reduced pressure and the residue diluted with aqueous sodium hydroxide. The product was extracted with diethyl ether, the organic extracts washed with water, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The cis and trans isomers 67 and 70 were separated by column chromatography on silica gel eluting with a solvent mixture of diethyl ether, petroleum spirits (bp 60-80°C) and triethylamine in the ratio 66:33:1, and the eluent was removed under reduced pressure to leave an oil. Compound 75 was purified by column chromatography on silica gel eluting with chloroform and methanol (1:1), and concentrated under reduced pressure. The remaining oil was converted to oxalate salt by dissolving in a small amount of absolute ethanol and adding a solution of two equivalents of oxalic acid in absolute ethanol. If no precipitate appeared, diethyl ether was added to form a precipitate. The solid was washed with diethyl ether and recrystallised from absolute ethanol.

METHOD L:

[0076] In a three-neck flask kept under nitrogen was placed a solution of the suitable 4'-hydroxyphenyl ketone (0.9 to 3 mmol), 3-(1-piperidinyl)propanol (0.9 to 3 mmol), and triphenyl phosphine (1 to 3.5 mmol) in 10 ml freshly distilled tetrahydrofuran. The mixture was stirred and cooled to 0°C with an ice and salt bath. A solution of diethyl azodicarboxylate (1 to 3.6 mmol) in 10 ml tetrahydrofuran was added very slowly (typically over 40 minutes) and the mixture was allowed to warm to room temperature after which it was stirred overnight at room temperature (16 hours). The solvent was then removed under reduced pressure, the residue dissolved in ethyl acetate (20 ml) and the product extracted with 2N HCl (2x10 ml). The aqueous solution was neutralised with sodium hydroxide and the product extracted with dichlorometh-

ane. After drying over magnesium sulphate and filtration, the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with diethyl ether containing 1 % triethylamine, and concentrated under reduced pressure. The residue was converted to oxalate salt by dissolving in a small amount of absolute ethanol and adding a solution of two equivalents oxalic add in absolute ethanol. If no precipitate appeared, diethyl ether was added to form a precipitate. The solid was washed with diethyl ether and recrystallised from absolute ethanol.

Pharmacological study

[0077] Interaction of compounds with the H_3 receptor are evidenced *in vitro* by the measurement of the release of neosynthesized tritiated histamine from rat cerebral cortex synaptosomes preincubated with tritiated histidine (Garbarg et al., J. Pharmacol. Exp. Ther., 1992, 263: 304-310). The H_3 potency of compounds is measured by the progressive reversal of the tritiated histamine release inhibition by the selective H_3 agonist (R)α-methylhistamine (Arrang et al., Nature, 1987, 327: 117-123).

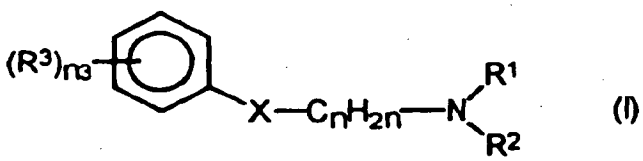
[0078] The effects of antagonists were estimated *in vivo* by the measurement of the tele-methylhistamine level variations in the brain of mice (Garbarg et al., J. Neurochem., 1989, 53: 1724-1730). At various time after p.o. administration of the compound, the effect of the H_3 antagonist is evidenced by the increase in the telemethylhistamine level induced. This increase is compared to the maximal effect induced by the reference H_3-antagonist thioperamide given at th dose of 10 mg/kg, p.o. This allows the calculation of the ED_{50} value for each compound which correspond to the dos responsible for an half maximal effect.

[0079] The results are reported in the following table II:

Ex No.	X	n	R^1R^2	R^3 (n_3 = 1)	Ki(nM)	ED_{50} (mg/kg/p.o.)
18	O	5	-$(CH_2)_4$-	p-NO_2	39±11	1.1
43	O	3	Et, Et	p-CN	95±28	0.50
46	O	3	Et, Et	p-CH_3CO		0.44
50	O	5	-$(CH_2)_4$-	p-$CH_3CH(OH)$		1.0
56	O	4	Et, Et	p-CN		1.1
59	O	3	-$(CH_2)_5$-	p-CN		0.20
60	O	3	-$(CH_2)_6$-	p-CN		0.64
63	O	3	Et, Et	p-$CH_3CH(OH)$		0.34
64	O	3	Et, Et	p-CH_3C=N(OH)		0.8
66	O	3	-(3-Me)-$(CH_2)_5$-	p-CH_3CO		0.3
68	O	3	-(4-Me)-$(CH_2)_5$-	p-CH_3CO		0.3
69	O	3	-$(CH_2)_5$-	p-C_2H_5CO		0.4

Claims

1. Compound of general formula (I) in which:



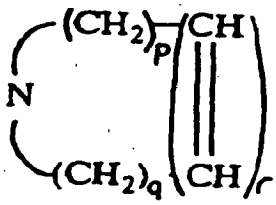
(I)

— C_nH_{2n} is a linear or branched hydrocarbon chain with n ranging from 2 to 8;
— X is an oxygen or sulfur atom;
— R^1 and R^2 may be identical or different and represent each independently

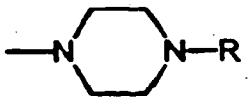
- a lower alkyl or cycloalkyl, or taken together with the nitrogen atom to which they are attached,
- a saturated nitrogen-containing ring

i) 

with m ranging from 4 to 7, or
- an unsaturated nitrogen-containing ring

ii) 

with p, q and r being 1 to 3 independently, such nitrogen-containing ring i) or ii) being unsubstituted or substituted by one or more lower alkyl or cycloalkyl, or carboalkoxy groups, or
- a morpholino group, or
- a N-substituted piperazino group:



with R being a lower alkyl, an alkanoyl or an optionally substituted phenyl group;

— n_3 is an integer from 0 to 5;
— R^3 represents each independently

- a halogen atom,
- a lower alkyl or cycloalkyl, a trifluoromethyl, aryl, alkoxy, aryloxy, nitro, formyl, alkanoyl, aroyl, arylalkanoyl, amino, carboxamido, cyano, alkyloximino, aryloximino, α-hydroxyalkyl, alkenyl, alkynyl, sulphamido, sulfamoyl, carboxamide, carboalkoxy, arylalkyl or oxime group,
- or taken together with the carbon atoms of the phenyl ring to which it is fused, a 5- or 6-membered saturated or unsaturated ring or a benzene ring,

as well as their pharmaceutically acceptable salts, their hydrates, their hydrated salts, the polymorphic crystalline structures of these compounds and their optical isomers, racemates, diastereoisomers and enantiomers, except compounds in which

- $-NR^1R^2$ is a pyrrolidinyl group, C_nH_{2n} is a linear chain $-(CH_2)_n-$ and n_3 is zero, X being an oxygen atom with n ranging from 3 to 5, or X being a sulfur atom with n being 4 or 5;
- $-NR^1R^2$ is a piperidinyl group, C_nH_{2n} is a linear chain $-(CH_2)_n-$ and and X is an oxygen atom, n_3 being zero with n being 2, 5 or 8 or n_3 being 1 with R^3 being 4-CN and n being 5;
- $-NR^1R^2$ is a diethylamine group, X is an oxygen atom, C_nH_{2n} is a linear chain $-(CH_2)_n-$ and n_3 is 1, R^3 being 4-

NO_2 or 4-$COCH_3$ with n being 3 or R^3 being 4-CN with n being 2 to 4;

- $-NR^1R^2$ is a dimethylamine group, X is an oxygen atom, C_nH_{2n} is a linear chain $-(CH_2)_n-$ and n^3 is 1, R^3 being 4-CN with n being 3.

2. Compound according to claim 1, in which R^1 and R^2 are independently a lower alkyl group.

3. Compound according to claim 2, in which R^1 and R^2 are each an ethyl group.

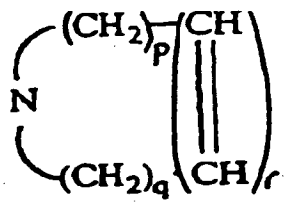
4. Compound according to claim 1, in which $-NR^1R^2$ is a saturated nitrogen-containing ring: m being as

i) 

defined in claim 1.

5. Compound according to claim 4, characterized in that m is 4, 5 or 6.

6. Compound according to claim 1, characterized in that $-NR^1R^2$ is an unsaturated nitrogen-containing ring:

ii) 

p, q and r being as defined in claim 1, preferably p, q and r are 1 or 2, more preferably p is 2 and q and r are 1.

7. Compound according to anyone of claims 4 to 6, characterized in that the nitrogen-containing ring i) or ii) is unsubstituted.

8. Compound according to anyone of claim 4 to 6, characterized in that the nitrogen-containing ring i) or ii) is substituted, preferably mono-substituted with an alkyl group.

9. Compound according to claim 8, characterized in that the nitrogen-containing ring is mono-substituted with a methyl group.

10. Compound according to claim 1, characterized in that $-NR^1R^2$ is a morpholino group.

11. Compound according to claim 1, characterized in that $-NR^1R^2$ is a N-substituted piperazino group, preferably N-acetylpiperazino.

12. Compound according to anyone of claims 1 to 11, characterized in that n_3 is zero.

13. Compound according to anyone of claims 1 to 11, characterized in that n_3 is 1 with R^3 being as defined in claim 1 and preferably in para-position.

14. Compound according to anyone of claims 1 to 11 and 13, characterized in that R^3 is a lower alkyl, preferably a C_1-C_4 alkyl.

15. Compound according to anyone of claims 1 to 11 and 13, characterized in that R^3 is a halogen atom, a cyano, nitro, alkanoyl, alkyloximine or hydroxyalkyl, preferably CN, NO_2, $COCH_3$, COC_2H_5, H_3C-C=N-OH or H_3C-CHOH.

16. Compound according to anyone of claims 1 to 11, characterized in that R^3 taken together with the carbon atoms of the phenyl group to which it is fused, form a 5- or 6- membered saturated or unsaturated ring, in particular a 5,6,7,8-tetrahydronaphthyl group.

17. Compound according to anyone of claims 1 to 11, characterized in that R^3 taken together with the phenyl group to which it is fused, form a naphthyl group.

18. Compound according to anyone of claims 1 to 17, characterized in that $-C_nH_{2n}-$ is a linear hydrocarbon chain $-(CH_2)_n-$, n being as defined in claim 1.

19. Compound according to anyone of claims 1 to 18, characterized in that X is an oxygen atom.

20. Compound according to anyone of claims 1 to 18, characterized in that X is a sulfur atom.

21. Compound according to anyone of claims 1 to 20, characterized in that n is varying from 3 to 5 and is preferably 3.

22. Compound according to anyone of claims 1 to 21, characterized in that it is one of the following compounds:

N-methyl-N-(5-phenoxypentyl)-ethylamine
1-(5-phenoxypentyl)-morpholine
N-(5-phenoxypentyl)-hexamethyleneimine
N-ethyl-N-(5-phenoxypentyl)-propylamine
1-(5-phenoxypentyl)-2-methyl-piperidine
1-(5-phenoxypentyl)-4-propyl-piperidine
1-(5-phenoxypentyl)-4-methyl-piperidine
1-(5-phenoxypentyl)-3-methyl-piperidine
1-acetyl-4-(5-phenoxypentyl)-piperazine
1-(5-phenoxypentyl)-3,5-trans-dimethyl-piperidine
1-(5-phenoxypentyl)-3,5-cis-dimethyl-piperidine
1-(5-phenoxypentyl)-2,6-cis-dimethyl-piperidine
4-carboethoxy-1-(5-phenoxypentyl)-piperidine
3-carboethoxy-1-(5-phenoxypentyl)-piperidine
1-(5-phenoxypentyl)-1,2,3,6-tetrahydropyridine
1-[5-(4-nitrophenoxy)-pentyl]-pyrrolidine
1-[5-(4-chlorophenoxy)-pentyl]-pyrrolidine
1-[5-(4-methoxyphenoxy)-pentyl]-pyrrolidine
1-[5-(4-methylphenoxy)-pentyl]-pyrrolidine
1-[5-(4-cyanophenoxy)-pentyl]-pyrrolidine
1-[5-(2-naphthyloxy)-pentyl]-pyrrolidine
1-[5-(1-naphthyloxy)-pentyl]-pyrrolidine
1-[5-(3-chlorophenoxy)-pentyl]-pyrrolidine
1-[5-(4-phenylphenoxy)-pentyl]-pyrrolidine
1-{5-[2-(5,6,7,8-tetrahydronaphthyl)-oxy]-pentyl}-pyrrolidine
1-[5-(3-phenylphenoxy)-pentyl]-pyrrolidine
1-(5-phenoxypentyl)-2,5-dihydropyrrole
1-{5-[1-(5,6,7,8-tetrahydronaphthyl)-oxy]-pentyl}-pyrrolidine
1-(6-phenoxyhexyl)-pyrrolidine
1-[5-(3-nitrophenoxy)-pentyl]-pyrrolidine
1-[5-(4-fluorophenoxy)-pentyl]-pyrrolidine
1-[5-(4-nitrophenoxy)-pentyl]-3-methyl-piperidine
1-[5-(4-acetylphenoxy)-pentyl]-pyrrolidine
1-[5-(4-aminophenoxy)-pentyl]-pyrrolidine
1-[5-(3-cyanophenoxy)-pentyl]-pyrrolidine
1-[5-(4-benzoylphenoxy)-pentyl]-pyrrolidine
1-{5-[4-(phenylacetyl)-phenoxy]-pentyl}-pyrrolidine
1-[5-(4-acetamidophenoxy)-pentyl]-pyrrolidine
1-[5-(4-phenoxyphenoxy)-pentyl]-pyrrolidine
1-[5-(4-N-benzamidophenoxy)-pentyl]-pyrrolidine

1-[5-(4-(1-hydroxyethyl)-phenoxy]-pentyl)-pyrrolidine
1-[5-(4-cyanophenoxy)-pentyl]-diethylamine
N-[5-(4-cyanophenoxy)-pentyl]-dimethylamine
N-[5-(4-cyanophenoxy)-pentyl]-dipropylamine
1-[3-(4-cyanophenoxy)-propyl]-pyrrolidine
1-[3-(4-cyanophenoxy)-propyl]-piperidine
N-[3-(4-cyanophenoxy)-propyl]-hexamethyleneimine
N-[6-(4-cyanophenoxy)-hexyl]-diethylamine
N-[3-(4-cyanophenoxy)-propyl]-dipropylamine
N-3-[4-(1-hydroxyethyl)-phenoxy]-propyl-diethylamine
4-(3-diethylaminopropoxy)-acetophenone-oxime
1-[3-(4-acetylphenoxy)-propyl]-piperidine
1-[3-(4-acetylphenoxy)-propyl]-3-methyl-piperidine
1-[3-(4-acetylphenoxy)-propyl]-3,5-trans-dimethyl-piperidine
1-[3-(4-acetylphenoxy)-propyl]-4-methyl-piperidine
1-[3-(4-propionylphenoxy)-propyl]-piperidine
1-[3-(4-acetylphenoxy)-propyl]-3,5-cis-dimethyl-piperidine
1-[3-(4-formylphenoxy)-propyl]-piperidine
1-[3-(4-isobutyrylphenoxy)-propyl]-piperidine
N-[3-(4-propionylphenoxy)-propyl]-diethylamine
1-[3-(4-butyrylphenoxy)-propyl]-piperidine
1-[3-(4-acetylphenoxy)-propyl]-1,2,3,6-tetrahydropyridine

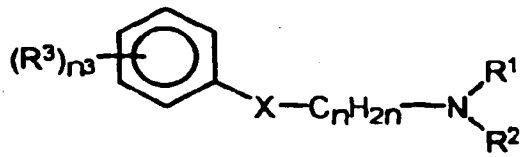
23. Compound according to anyone of claims 1 to 22, characterized in that it is one of the following compounds:

1-[5-(4-nitrophenoxy)-pentyl]-pyrrolidine
1-{5-[4-(1-hydroxyethyl)-phenoxy]-pentyl}-pyrrolidine
1-[3-(4-cyanophenoxy)-propyl]-piperidine
N-[3-(4-cyanophenoxy)-propyl]-hexamethyleneimine
N-3-[4-(1-hydroxyethyl)-phenoxy]-propyl-diethylamine
4-(3-diethylaminopropoxy)-acetophenone-oxime
1-[3-(4-acetylphenoxy)-propyl]-3-methyl-piperidine
1-[3-(4-acetylphenoxy)-propyl]-4-methyl-piperidine
1-[3-(4-propionylphenoxy)-propyl]-piperidine

24. Pharmaceutical composition characterized in that it comprises as active ingredient, a therapeutically effective amount of a compound according to anyone of claim 1 to 23 in combination with a pharmaceutically acceptable vehicle or excipient.

25. Medicament acting as an antagonist of the histamine H_3-receptors, characterized in that it comprises as active ingredient, an effective amount of a compound according to anyone of claims 1 to 23.

26. Use of a compound of general formula (I) in which:



(I)

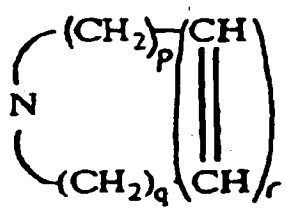
— C_nH_{2n} is a linear or branched hydrocarbon chain with n ranging from 2 to 8;
— X is an oxygen or sulfur atom;
— R^1 and R^2 may be identical or different and represent each independently

- a lower alkyl or cycloalkyl, or taken together with the nitrogen atom to which they are attached,
- a saturated nitrogen-containing ring

i) 

with m ranging from 4 to 7, or

- an unsaturated nitrogen-containing ring

ii) 

with p, q and r being 1 to 3 independently, such nitrogen-containing ring i) or ii) being unsubstituted or substituted by one or more lower alkyl or cycloalkyl, or carboalkoxy groups, or

- a morpholino group, or
- a N-substituted piperazino group:

with R being a lower alkyl, an alkanoyl or an optionally substituted phenyl group;

— n_3 is an integer from 0 to 5;
— R^3 represents each independently

- a halogen atom,
- a lower alkyl or cycloalkyl, a trifluoromethyl, aryl, alkoxy, aryloxy, nitro, formyl, alkanoyl, aroyl, arylalkanoyl, amino, carboxamido, cyano, alkyloximino, aryloximino, α-hydroxyalkyl, alkenyl, alkynyl, sulphamido, sulfamoyl, carboxamide, carboalkoxy, arylalkyl or oxime group,
- or taken together with the carbon atoms of the phenyl ring to which it is fused, a 5- or 6-membered saturated or unsaturated ring or a benzene ring.

as well as their pharmaceutically acceptable salts, their hydrates, their hydrated salts, the polymorphic crystalline structures of these compounds and their optical isomers, racemates, diastereoisomers and enantiomers, for the preparation of a medicament acting as an antagonist of the histamine H_3-receptors.

27. Use according to claim 26, characterized in that compound (I) is as defined in any one of claims 2 to 21.

28. Use according to claim 26 characterized in that compound (I) is one of the following compounds:

1-(5-phenoxypentyl)-piperidine
1-(5-phenoxypentyl)-pyrrolidine
N-methyl-N-(5-phenoxypentyl)-ethylamine
1-(5-phenoxypentyl)-morpholine
N-(5-phenoxypentyl)-hexamethyleneimine
N-ethyl-N-(5-phenoxypentyl)-propylamine
1-(5-phenoxypentyl)-2-methyl-piperidine

1-(5-phenoxypentyl)-4-propyl-piperidine
1-(5-phenoxypentyl)-4-methyl-piperidine
1-(5-phenoxypentyl)-3-methyl-piperidine
1-acetyl-4-(5-phenoxypentyl)-piperazine
1-(5-phenoxypentyl)-3,5-trans-dimethyl-piperidine
1-(5-phenoxypentyl)-3,5-cis-dimethyl-piperidine
1-(5-phenoxypentyl)-2,6-cis-dimethyl-piperidine
4-carboethoxy-1-(5-phenoxypentyl)-piperidine
3-carboethoxy-1-(5-phenoxypentyl)-piperidine
1-(5-phenoxypentyl)-1,2,3,6-tetrahydropyridine
1-[5-(4-nitrophenoxy)-pentyl]-pyrrolidine
1-[5-(4-chlorophenoxy)-pentyl]-pyrrolidine
1-[5-(4-methoxyphenoxy)-pentyl]-pyrrolidine
1-[5-(4-methylphenoxy)-pentyl]-pyrrolidine
1-[5-(4-cyanophenoxy)-pentyl]-pyrrolidine
1-[5-(2-naphthyloxy)-pentyl]-pyrrolidine
1-[5-(1-naphthyloxy)-pentyl]-pyrrolidine
1-[5-(3-chlorophenoxy)-pentyl]-pyrrolidine
1-[5-(4-phenylphenoxy)-pentyl]-pyrrolidine
1-{5-[2-(5,6,7,8-tetrahydronaphthyl)-oxy]-pentyl}-pyrrolidine
1-[5-(3-phenylphenoxy)-pentyl]-pyrrolidine
1-(5-phenoxypentyl)-2,5-dihydropyrrole
1-{5-[1-(5,6,7,8-tetrahydronaphthyl)-oxy]-pentyl}-pyrrolidine
1-(4-phenoxybutyl)-pyrrolidine
1-(6-phenoxyhexyl)-pyrrolidine
1-(5-phenylthiopentyl)-pyrrolidine
1-(4-phenylthiobutyl)-pyrrolidine
1-(3-phenoxypropyl)-pyrrolidine
1-[5-(3-nitrophenoxy)-pentyl]-pyrrolidine
1-[5-(4-fluorophenoxy)-pentyl]-pyrrolidine
1-[5-(4-nitrophenoxy)-pentyl]-3-methyl-piperidine
1-[5-(4-acetylphenoxy)-pentyl]-pyrrolidine
1-[5-(4-aminophenoxy)-pentyl]-pyrrolidine
1-[5-(3-cyanophenoxy)-pentyl]-pyrrolidine
N-[3-(4-nitrophenoxy)-propyl]-diethylamine
N-[3-(4-cyanophenoxy)-propyl]-diethylamine
1-[5-(4-benzoylphenoxy)-pentyl]-pyrrolidine
1-{5-[4-(phenylacetyl)-phenoxy]-pentyl}-pyrrolidine
N-[3-(4-acetylphenoxy)-propyl]-diethylamine
1-[5-(4-acetamidophenoxy)-pentyl]-pyrrolidine
1-[5-(4-phenoxyphenoxy)-pentyl]-pyrrolidine
1-[5-(4-N-benzamidophenoxy)-pentyl]-pyrrolidine
1-{5-[4-(1-hydroxyethyl)-phenoxy]-pentyl}-pyrrolidine
1-[5-(4-cyanophenoxy)-pentyl]-diethylamine
1-[5-(4-cyanophenoxy)-pentyl]-piperidine
N-[5-(4-cyanophenoxy)-pentyl]-dimethylamine
N-[2-(4-cyanophenoxy)-ethyl]-diethylamine
N-[3-(4-cyanophenoxy)-propyl]-dimethylamine
N-[4-(4-cyanophenoxy)-butyl]-diethylamine
N-[5-(4-cyanophenoxy)-pentyl]-dipropylamine
1-[3-(4-cyanophenoxy)-propyl]-pyrrolidine
1-[3-(4-cyanophenoxy)-propyl]-piperidine
N-[3-(4-cyanophenoxy)-propyl]-hexamethyleneimine
N-[6-(4-cyanophenoxy)-hexyl]-diethylamine
N-[3-(4-cyanophenoxy)-propyl]-dipropylamine
N-3-[4-(1-hydroxyethyl)-phenoxy]-propyl-diethylamine
4-(3-diethylaminopropoxy)-acetophenone-oxime
1-[3-(4-acetylphenoxy)-propyl]-piperidine

1-[3-(4-acetylphenoxy)-propyl]-3-methyl-piperidine
1-[3-(4-acetylphenoxy)-propyl]-3,5-trans-dimethyl-piperidine
1-[3-(4-acetylphenoxy)-propyl]-4-methyl-piperidine
1-[3-(4-propionylphenoxy)-propyl]-piperidine
1-[3-(4-acetylphenoxy)-propyl]-3,5-cis-dimethyl-piperidine
1-[3-(4-formylphenoxy)-propyl]-piperidine
1-[3-(4-isobutyrylphenoxy)-propyl]-piperidine
N-[3-(4-propionylphenoxy)-propyl]-diethylamine
1-[3-(4-butyrylphenoxy)-propyl]-piperidine
1-[3-(4-acetylphenoxy)-propyl]-1,2,3,6-tetrahydropyridine

29. Use according to claim 26, characterized in that compound (I) is one of the following compounds:

1-[5-(4-nitrophenoxy)-pentyl]-pyrrolidine
N-[3-(4-cyanophenoxy)-propyl]-diethylamine
N-[3-(4-acetylphenoxy)-propyl]-diethylamine
1-[5-[4-(1-hydroxyethyl)-phenoxy]-pentyl]-pyrrolidine
N-[4-(4-cyanophenoxy)-butyl]-diethylamine
1-[3-(4-cyanophenoxy)-propyl]-piperidine
N-[3-(4-cyanophenoxy)-propyl]-hexamethyleneimine
N-3-[4-(1-hydroxyethyl)-phenoxy]-propyl-diethylamine
4-(3-diethylaminopropoxy)-acetophenone-oxime
1-[3-(4-acetylphenoxy)-propyl]-3-methyl-piperidine
1-[3-(4-acetylphenoxy)-propyl]-4-methyl-piperidine
1-[3-(4-propionylphenoxy)-propyl]-piperidine

30. Medicament according to anyone of claims 25 to 29, for the treatment of central nervous system disorders, in particular Alzheimer disease, mood and attention alterations, cognitive deficits in psychiatric pathologies, obesity, vertigo and motion sickness.

31. Medicament according to anyone of claims 25 to 29, having psychotropic effects, promoting wakefulness, attention, memory and improving mood, intended to be used in particular in the treatment of Alzheimer disease and other cognitive disorders in aged persons, depressive or asthenic states.

32. Medicament according to anyone of claims 25 to 29, having nootropic effects, intended to be used in particular in treatment to stimulate attention and memorization capacity.

33. Medicament according to anyone of claims 25 to 29, for the treatment of obesity, vertigo and motion sickness.

34. Medicament according to anyone of claims 25 to 29, for the treatment of CNS disorders, in particular of aged persons.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 98 40 1944

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	GB 1 512 880 A (MITSUBISHI CHEM IND) 1 June 1978 * examples; table I * ---	1-24	C07D295/088 C07C211/08 C07D211/04 C07D295/185 C07D211/62 C07D211/70 C07D207/20 A61K31/13 A61K31/40 A61K31/445 A61K31/495
X	DE 12 69 134 B (VEB DEUTSCHES HYDRIERWERK RODLEBEN) 18 December 1962 * examples 1-5 * ---	1-24	
X	US 3 947 434 A (SPENCER CLAUDE F ET AL) 30 March 1976 * examples LXXIXA,B * ---	1-24	
X	US 4 751 302 A (IBUKI TADAYUKI ET AL) 14 June 1988 * tables 5-2,5-3 * ---	1-24	
X	GB 924 961 A (THE WELLCOME FOUNDATION LIMITED) 1 May 1963 * table II * ---	1-24	
X	US 3 312 696 A (TURBANTI L.) 4 April 1967 * claim 1; examples 1-20 * --- -/--	1-24	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07D
C07C
A61K

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
MUNICH	7 December 1998	Juntunen, A

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 98 40 1944

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	DE 26 24 261 A (BOTTU FA) 16 December 1976 * page 4; example 10 * ---	1-24	
X	US 2 870 151 A (WRIGHT H.B. AND MOORE M.B.) 20 January 1959 * examples I-XII * ---	1-24	
X	DE 965 813 C (ABBOTT LABORATORIES) 19 June 1957 * examples 1-5,7 * ---	1-24	
X	LITTMANN E. R. AND MARVEL C. S.: "Cyclic Quaternary Ammonium Salts from Halogenated Aliphatic Tertiary Amines" J.AMER.CHEM.SOC., vol. 52, 1930, pages 287-294, XP002084866 * page 289 - page 290 * ---	1-24	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
X	KIKUMOTO R. ET AL.: "Synthesis and Antidepressant Activity of Substituted (gamma-Aminoalkoxy)benzene Derivatives" J.MED.CHEM., vol. 24, no. 2, 1981, pages 145-148, XP000565653 * table 1 * ---	1-26	
X	SHADBOLT R. S. ET AL.: "Some Aryloxyalkylamines, N-Arylethylenediamines and Related Compounds as Anorectic Agents" J.MED.CHEM., vol. 14, no. 9, 1971, pages 836-842, XP002084867 * table 1 * --- -/--	1-24	

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 98 40 1944

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	WALSH D. A. ET AL.: "Synthesis and Antiallergy Activity of 4-(Diarylhydroxymethyl)-1-[3-(aryloxy)propyl]piperidines and Structurally Related Compounds" J.MED.CHEM., vol. 32, no. 1, 1989, pages 105-118, XP002084868 * tables I-III * ---	1-24	
X	SOHDA T ET AL: "STUDIES ON ANTIDIABETIC AGENTS. SYNTHESIS OF 5-4-(1-METHYLCYCLOHEXYLMETHOXY)-BENZYL)THIAZOLIDINE-2,4-DIONE (ADD-3878) AND ITS DERIVATIVES" CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 30, no. 10, 1982, pages 3580-3600, XP002046259 * table VIII * ---	1-24	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
X	CHABRIER P. ET AL.: "Nouveaux carbamates doués d'activité anesthésique locale" BULL.SOC.CHIM.FR.,1955, pages 1353-1357, XP002084869 * table IV * ---	1-24	
X	MARQUET J. ET AL.: "Topologically Controlled Coulombic Interactions, a New Tool in the Developing of Novel Reactivity. Photochemical and Electrochemical Cleavage of Phenyl Alkyl Ethers" J.ORG.CHEM., vol. 60, no. 12, 1995, pages 3814-3825, XP002084870 * table 1 * --- -/--	1-24	

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 98 40 1944

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	CASANOVAS A.-M. ET AL.: "Etude des relations structure-activté d'une série d'anesthésiques locaux" EUR.J.MED.CHEM.-CHIM.THER., vol. 17, no. 4, 1982, pages 333-337, XP002084871 * page 334 *	1-24	
X	KIKUMOTO R ET AL: "SYNTHESES AND PLATELET AGGREGATION INHIBITORY AND ANTITHROMBOTIC PROPERTIES OF 2-(OMEGA-AMINOALKOXY)PHENYLETHYLBENZENES" JOURNAL OF MEDICINAL CHEMISTRY, vol. 33, no. 6, June 1990, pages 1818-1823, XP000673455 * tables I-III *	1-24	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
X	CHENEY L.C. ET AL.: "Alkylaminoalkyl Ethers of the Benzylphenols" J.AMER.CHEM.SOC., vol. 71, 1949, pages 60-64, XP002086293 * page 60; table I *	1-26	
A	STARK H. ET AL.: "Developments of Histamine H3-receptor Antagonists" DRUGS OF THE FUTURE, vol. 21, no. 5, 1996, pages 507-520, XP002084872 * page 507 *	1-34	

EPO FORM 1503 03.82 (P04C19)

European Patent Office

INCOMPLETE SEARCH
SHEET C

Application Number
EP 98 40 1944

Claim(s) searched incompletely:
1-34

Reason for the limitation of the search:

The search on the final compounds of a restricted subset of formula I (R1 and R2= a lower alkyl, a saturated N-containing ring, a morpholino group, a N-substituted piperazino group as defined in claim 1) and their histamine H3-receptor antagonistic activity revealed already a vast amount of novelty destroying compounds with respect to claim 1 of the present application. Therefore the search had to be limited to the compounds of claims 2 and 5 encompassed by the above defined subset, and to the activity thereof.

Despite the above limitation to the two groups of compounds the search revealed too many relevant documents and/or compounds so that the search report shall not be considered complete.

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 98 40 1944

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

07-12-1998

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 1512880 A	01-06-1978	JP 1233459 C	26-09-1984
		JP 52000248 A	05-01-1977
		JP 59008265 B	23-02-1984
		US 4024282 A	17-05-1977
		CH 623301 A	29-05-1981
		DE 2627227 A	30-12-1976
		DK 276276 A,B,	20-12-1976
		FR 2315913 A	28-01-1977
		NL 7606668 A,B,	21-12-1976
		SE 430156 B	24-10-1983
		SE 7607013 A	20-12-1976
		US 4071559 A	31-01-1978
		JP 1258356 C	29-03-1985
		JP 52033635 A	14-03-1977
		JP 59035386 B	28-08-1984
		US 4061776 A	06-12-1977
		JP 1283612 C	27-09-1985
		JP 52033658 A	14-03-1977
		JP 60006349 B	18-02-1985
		US 4091114 A	23-05-1978
		JP 1323708 C	27-06-1986
		JP 52057133 A	11-05-1977
		JP 60048507 B	28-10-1985
		US 4060612 A	29-11-1977
		BE 848612 A	23-05-1977
		JP 1356666 C	13-01-1987
		JP 52065254 A	30-05-1977
		JP 61020536 B	22-05-1986
		US 4060641 A	29-11-1977
		JP 1256359 C	12-03-1985
		JP 52085156 A	15-07-1977
		JP 59031492 B	02-08-1984
		US 4100299 A	11-07-1978
DE 1269134 B		NONE	
US 3947434 A	30-03-1976	US 3919238 A	11-11-1975
		AU 475718 B	02-09-1976
		AU 6523674 A	04-09-1975
		BE 816003 A	06-12-1974
		DE 2427409 A	09-01-1975
		DK 301974 A,B,	03-02-1975
		FR 2232313 A	03-01-1975
		GB 1398508 A	25-06-1975
		IL 44141 A	31-08-1976
		JP 50019777 A	01-03-1975

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 98 40 1944

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

07-12-1998

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3947434 A		NL 7404135 A	10-12-1974
		SE 391925 B	07-03-1977
		SE 7405652 A	09-12-1974
		ZA 7400683 A	24-09-1975
US 4751302 A	14-06-1988	JP 58159471 A	21-09-1983
		JP 58159472 A	21-09-1983
		JP 58159473 A	21-09-1983
		JP 58159474 A	21-09-1983
		JP 58159475 A	21-09-1983
		JP 58159476 A	21-09-1983
		JP 58159477 A	21-09-1983
		EP 0090972 A	12-10-1983
		US 4533731 A	06-08-1985
GB 924961 A		BE 588558 A	
		CH 361005 A	
		CH 395126 A	
		CH 436259 A	
		DE 1238485 B	
		FR 558 M	
		FR 84256 E	05-05-1965
		FR 1421206 A	09-03-1966
		GB 824853 A	
		GB 921978 A	
		LU 38374 A	
		NL 129619 C	
		NL 249341 A	
US 3312696 A	04-04-1967	NONE	
DE 2624261 A	16-12-1976	FR 2313042 A	31-12-1976
		FR 2349332 A	25-11-1977
		BE 842453 A	01-10-1976
		CH 597192 A	31-03-1978
		GB 1513092 A	07-06-1978
US 2870151 A		NONE	
DE 965813 C		NONE	

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82